Trends in Neurosciences

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Review

Tapping into Multi-Faceted Human Behavior and Psychopathology Using fMRI Brain Dynamics

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Human behavior comprises many aspects that stand out by their dynamic nature. To quantify its neural underpinnings, time-resolved fMRI methods have blossomed over the past decade. In this review we conceptually organize a broad repertoire of dynamic analytical pipelines and extract general observations on their application to the study of behavior and brain disorders. We aim to provide an extensive overview instead of examining only selected methodological families or specific behavioral domains. We consider behavioral aspects with distinct long-term stability (e.g., physiological state versus personality), and also address selected brain disorders with complementary genetics and symptomatology. This synthesis exposes the somewhat limited consistency of dynamic findings in the literature, as well as the unbalanced application of the multitude of available approaches which would, owing to their technical specificities, have potential to reveal distinct aspects of dynamics. We call for further comparative and collaborative efforts in the future.

Highlights

The human brain is a dynamic system, giving rise to behavioral facets that fluctuate at distinctive time-scales. Alterations of dynamic neural processing, as seen in brain disorders, can lead to perturbed behavior.

We conceptually relate fMRI methodologies for quantifying dynamic functional connectivity, and review their application to the study of healthy behavior and its alterations in autism, schizophrenia, and depression.

Each method probes regional activity or cross-regional interactions at a given spatiotemporal resolution, focusing on the whole brain or on dedicated areas, and encodes dynamics with a specific complexity.

On the whole, analytical outcomes are difficult to relate across studies, and only a few methodologies are broadly leveraged by the research community.

Mechanistic models of brain dynamics, and large-scale collaborative and comparative efforts, are ways forward to circumvent these issues.

Brain Dynamics Inferred from Functional Neuroimaging Are Relevant to the Study of Human Behavior

Perhaps the most remarkable feature of humanity is the profound behavioral diversity across different individuals, which pertains to all factors involved in interactions with the physical and social environment. This diversity underlies variability in personality, physiology, and mental capacity, which in turn are not only constituted by biological influences (e.g., fatigue, the influence of drugs, genetic makeup) but also shaped by experience (e.g., social learning, trauma). Arguably, the brain is the most complex system known to humankind, and understanding this organ is crucial for explaining behavior. Studying the brain at rest has demonstrated that, although the environment has an influence on it, the brain operates intrinsically and is modulated rather than controlled by the environment [1]. This modulation is a recursive process between the brain and the environment mediated by perception and action [2]. Evidently, this process is highly dynamic, as are the environment and the brain [3].

Neuroscience, in particular neuroimaging research, aims to relate variability in behavior to changes in the brain. Since its discovery in the early 1990s, **functional magnetic resonance imaging** (fMRI; see Glossary) has become one of the most prominent methods to this end. fMRI is a non-invasive tool to probe whole-brain activity and enables the study of sophisticated processes that involve functional integration and segregation of different brain areas over time. The study of brain signals during task or other forms of stimulation has been a productive way to decode the representation of specific processes in the brain; however, studies on the intrinsic organization of the brain at rest are equally valuable, and have been shown to predict behavior and psychopathology [4,5].

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Original analysis approaches evolved in parallel with progress in acquisition technology from harvesting regional activation to dispersed network connectivities, and until recently relied on static measures to understand brain function [6]. However, static measures fall short of capturing the inherent dynamic nature of both brain and behavior, and thus may be limited in their explanatory value and omit important insights. Consistent with the assumption that all aspects of behavior are dynamic phenomena, tailored analytical approaches to study the fMRI signals in a time-resolved manner have become increasingly prominent ([7,8] for methodological reviews). In addition, these methodologies have been applied to the study of cognition and psychiatric disorders (as reviewed in [9] for a subset of technical approaches).

In this review, compared with past reports, we offer a more comprehensive overview of both dynamic analytical pipelines and their application to a range of behaviors and disorders. To this end, we provide a characterization of the primarily derived measures of functional brain dynamics as well as a conceptual organization of a broad array of dynamic methodologies. We hope that this will be a useful orientation not only for researchers who are new to these methods, but also for those who are familiar with them. We then examine the use of dynamic methods across healthy and perturbed behavior, and investigate whether commonalities regarding the results from dynamic methods can be extracted. In doing so, we probe a set of behavioral aspects and examine complementary brain disorders in terms of their genetic characteristics and symptoms.

A few introductory remarks should be added. Although we include different aspects of behavior to discuss conceptually distinct methodologies, our coverage remains non-exhaustive owing to space constraints. In addition, in what follows we make the assumption that reported findings truly characterize neural substrates of behavior, which remains an open question in dynamic fMRI-based analyses (Box 1).

Box 1. Non-Neural Contributions to Dynamic fMRI-Based Brain/Behavior Analyses

To meaningfully probe the neural correlates of behavior through functional brain dynamics, one would hope that the acquired data accurately describe electrical brain activity; however, more than half of BOLD signal contributions are in fact non-neural [95]. More precisely, changes in head motion of the scanned volunteers, as well as respiratory and cardiac fluctuations, exert strong confounding impacts that many have attempted to attenuate through dedicated preprocessing steps ([96] for comprehensive review). Such choices can crucially influence the relationships between fMRI signals and behavior: for example, associations with resting-state functional connectivity are reinforced when the global signal (the fraction of the BOLD signal that varies similarly across the whole grey matter) is regressed out [97].

It remains uncertain whether current preprocessing strategies fully remove physiological confounds, given their insidious similarity to neural networks. Recently, respiratory variation and heart-rate changes were shown to induce spatiotemporally complex BOLD responses in segregated brain regions, in a way that mimicked resting-state networks [98]. In addition, fluctuations in end-tidal CO_2 (inducing vascular, as opposed to neural, changes in the brain) also yielded vascular equivalents to several notorious networks [99]. Because physiological rhythms are profoundly affected by many behavioral aspects, one may question the neural nature of BOLD-based behavioral correlates.

In addition, preprocessing may instead amputate the original signals from a behaviorally meaningful fraction. This has recently been suggested in the context of head motion: indeed, several overlapping spatiotemporal motion components were unraveled over the course of a recording session, and were linked to a broad array of behaviors [100]. Correcting for motion may thus partly remove behaviorally relevant information from the data.

Improvements in acquisition technology may help to reduce confounding impacts on the BOLD signals, while further favoring dynamic analyses. First, recording fMRI data at subsecond temporal resolution [101] enables a better separation between neural and physiological signal sources [102]. However, additional issues are also introduced: for example, estimates of head motion then become more strongly influenced by physiology [103], rendering a proper account of these two types of confound even more challenging. Second, through multi-echo acquisition, physiology-, and motion-induced confounds are further attenuated [104,105]. Dynamic analytical pipelines tailored to exploit the benefits provided by such data are emerging [106].

The Dynamics of Brain Activity Can Be Characterized in Diverse and Complementary Ways

Connection-Wise Variability and Connectivity States Are the Two Primarily Derived Measures of Functional Brain Dynamics

Given its simplicity, the sliding window framework has strengthened its position as the most widely applied tool to track the dynamics of brain activity [7]. This is illustrated in Figure 1 in its canonical form (discussed later); more recent technical developments and directly associated methods are addressed in Box 2. Briefly, the statistical interdependence between regional activity timecourses, termed **functional connectivity** (FC) [10], is evaluated across consecutive temporal windows of 30–60 s over the whole duration of the acquisition. The regional timecourses are generally obtained by averaging the voxel-wise functional signals within regions of a chosen brain parcellation, or within spatial clusters from **independent component analysis** (ICA). The outcome from a sliding window-based analysis is a set of timecourses that denote temporal changes in cross-regional interactions throughout the brain. The often-used **dynamic functional connectivity** (dFC) jargon originally denoted this type of time-resolved correlational information; it has since become an umbrella term that includes other families of methods, as developed later.

The two most widely applied dynamic measures in brain/behavior analyses are constructed from dFC timecourses. At the level of individual connections, one can quantify the standard deviation (or alternative variability metrics) of the timecourse [11,12]; we term this **connection-wise variability** (CV). At the whole-brain level, the clustering of connection timecourses concatenated across subjects instead leads to the identification of **connectivity states** (CS); namely recurring patterns of connectivity [13]. If the derived CS are assumed to be mutually exclusive in time, their occurrences and the rate of transitions across them characterize temporal dynamics [13]. If instead, the CS are jointly expressed, the construction of meta-states (weighted combinations of CS) enables investigation of the fluidity and dynamism of brain activity at a higher-order level [14].

Instead of an FC matrix, dFC measurements from a given temporal window can also be viewed as a whole-brain graph in which nodes are the regions, and edges are their current FC estimates. Dynamic **graph analysis** (GA) is then performed by tracking global properties reflective of information flow [15] or community organization [16] over time.

Categorizing dFC Methods Based on Their Conceptual Features

Figure 2 categorizes dFC methods (not only sliding window-based) in terms of their main conceptual features. First, different approaches investigate different features in the original functional data. Some approaches, for example, characterize the temporal activity of individual regions, whereas others (including the computation of CV or CS) probe the synchronicity of changes between distinct brain areas.

Second, each approach examines temporal fluctuations at a specific temporal resolution: it is intermediate for CV because it cannot be known whether an FC change happened from one frame to the next or at a slower pace. Instead, the extraction of CS relates to a faster temporal resolution: if a step size of 1 TR (repetition time) is used, more rapid changes can indeed be captured as sudden fluctuations in whole-brain FC.

Third, spatial resolution also differs across methods. For CS and CV, this depends on how the regional timecourses are built; for example, the original ICA-based scheme [13] would imply a network-level resolution. A concomitant point is the focus of the analyses; for example, whole-brain for canonical CS versus centered on a key area.

Glossary

Autism spectrum disorder (ASD): a spectrum of neurodevelopmental conditions characterized by socio-communicative impairments, abnormal responsiveness to sensory stimulation, and stereotyped behavior.
Blood oxygenation level-dependent (BOLD): the BOLD signal indirectly reflects the level of neural activity through neurovascular coupling.
Coactivation pattern (CAP): a whole-brain map of activity denoting the territories that co-(de)activate with a seed region of interest.
Connection-wise variability (CV): this quantifies (typically through standard deviation) the fluctuations of functional connectivity between two brain regions along consecutive time-windows.
Connectivity states (CS): short-lived patterns of whole-brain functional connectivity, which are mutually exclusive in terms of their temporal expression.
Default mode network (DMN): a set of synchronous areas recruited during different types of introspective processing, such as memory recollection or theory of mind.
Dynamic functional connectivity (dFC): this originally denoted the change in functional connectivity between pairs of brain regions with time, and has then become an umbrella term for all analytical approaches that attempt to characterize the dynamics of brain activity.
Functional connectivity (FC): a measure of the statistical interdependence between the activity timecourses of two brain regions, as most often computed through Pearson's correlation coefficient.
Functional magnetic resonance imaging (fMRI): a neuroimaging method that monitors the activity of the whole brain over the course of time.
Graph analysis (GA): the understanding of the brain as a network of structurally or functionally interconnected areas, from which measures reflective of information flow or community organization can be derived.
Hidden Markov model (HMM): a probabilistic description of data in which a causal relationship is hypothesized between successive states of the system examined (for example, fMRI volumes acquired at successive timepoints), and each state yields an

Finally, each method conveys dynamic information at a different level of complexity: for CV, each cross-regional interplay is encoded by only one number, whereas for CS there are *K* different values (one per state), and informative metrics are then generated through dedicated recombination processes, as touched upon earlier.

Alternative Analytical Approaches Refine Standard Tools along Several Conceptual Axes

Although CV and CS have been most prominently scrutinized in dynamic studies of the brain, they cover a limited area of the conceptual space that can be explored. Accordingly, alternative approaches have been introduced over the past years: for instance, the computation of **blood oxygenation level-dependent** (BOLD) signal variability [17] operates at a regional (rather than cross-regional) level, and one can also track (cross-)regional synchronization across subjects using the sliding window framework [18]. Note that for these approaches, one estimate is obtained per pair of subjects for a given connection.

Several frameworks specifically enhance temporal resolution by operating at a framewise level: in **leading eigenvector dynamics analysis** (LEiDA) [19], framewise information regarding the phase of regional activity is obtained through a Hilbert transform. Following extraction of the dominant cross-regional phase differences at each timepoint, clustering-derived states offer a different perspective on functional brain dynamics. In another methodology, **innovation-driven coactivation patterns** (iCAPs) are obtained by clustering the deconvolved fMRI volumes that show the largest whole-brain signal change [20]. Finally, **coactivation pattern** (CAP) analysis also yields patterns of whole-brain activity, but the focus is set on the interactions with a seed region of interest by retaining only the timepoints when it exceeds a threshold of activity [21].

Instead of treating temporal samples as separate entities, some methodologies jointly examine space and time: in multilayer GA, individual sliding window-based graphs are linked in time,

observed measurement (for instance, voxel-wise patterns of whole-brain activity).

Independent component analysis (ICA): an unsupervised data analysis approach that extracts statistically independent components from a dataset (in neuroimaging, ICA is most commonly used to derive spatially independent components from whole-brain BOLD timecourses).

Innovation-driven coactivation pattern (iCAP): a whole-brain map of activity denoting the spatial areas that jointly change their activity from one timepoint to the next.

Leading eigenvector dynamics analysis (LEiDA): a methodological pipeline that computes the phase difference between the activity of all brain regions, and extracts the dominant existing pattern at each timepoint.

Major depressive disorder (MDD): a psychiatric condition characterized by a persistent feeling of sadness and loss of interest in daily-life activities.

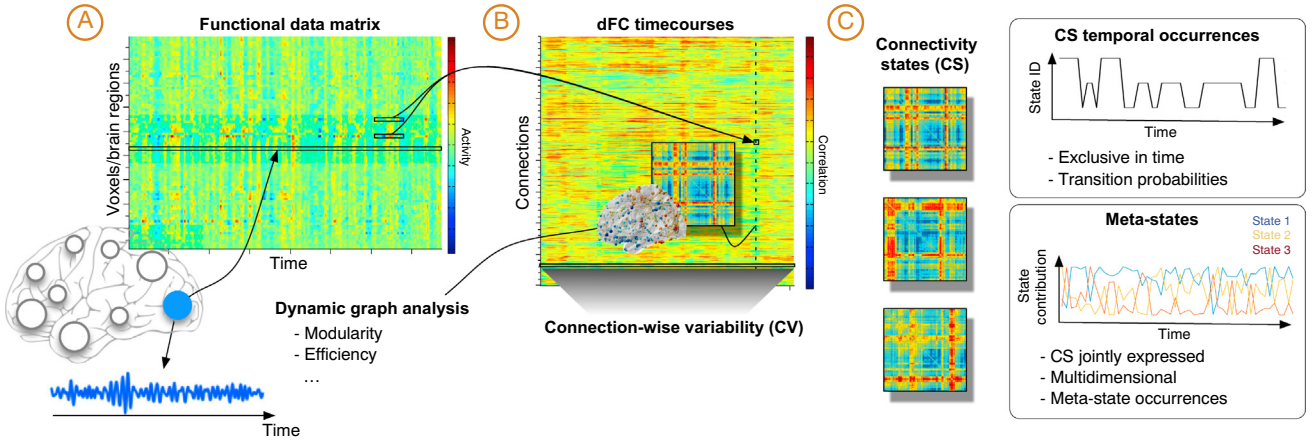

Figure 1. Canonical Sliding Window-Based Dynamic Functional Connectivity Measures. (A) Each brain region evolves in activity over time, as depicted by the rows of the functional data matrix. To infer statistical interdependence between a pair of regions (or alternatively voxels) at a given timepoint, a subset of activity samples are extracted within a temporal sub-window. (B) The computation of functional connectivity (FC) between these windowed segments yields one estimate of the dynamic FC (dFC) timecourse between the selected regions (i.e., for a given brain connection). A full timecourse is constructed by iteratively shifting the window over time. If the standard deviation of a timecourse is computed, the resulting extent of dFC variability over time is termed connection-wise variability (CV). If dFC timecourses are obtained for all pairs of regions, one timepoint of the resulting representation can be seen as a matrix denoting current whole-brain FC, or as a graph where nodes are the brain regions and FC estimates the edges. Dynamic graph analysis proceeds from a temporal series of such graphs, tracking changes in metrics such as modularity and efficiency. (C) If the dFC data are concatenated across subjects, they can be decomposed into summary building blocks that are reflective of short-lived whole-brain FC, known as connectivity states (CS). When CS are mutually exclusive in time, occurrences and transition probabilities are informative metrics. When they are jointly expressed in time, linear combinations of state expression are treated as the informative entities in a meta-state analysis.

Box 2. Improvements to Canonical Sliding Window dFC Analysis

Sliding window-based investigations can be tuned at several stages [7]. First, instead of fixed size rectangular windows, averaging across temporal neighbors has been suggested [107], and modulated rectangular windows were shown to more efficiently capture dFC metrics [108]. Time-varying window lengths were also proposed: stationarity with an initial length guess is assessed, and that length is iteratively increased until consistent stationarity across brain regions is achieved [109]. In other work, the BOLD standard deviation across regions was assessed to pinpoint moments putatively associated with a state transition [110].

To replace Pearson's correlation coefficient as the measure of FC, correlating two dFC timecourses (i.e., correlation of correlation timecourses) has been suggested, showcasing fair-to-moderate reliability [111]. Others have proposed to compute the first-order time derivatives between dFC estimates together with dFC itself, using finite difference approximations [112]. Framewise estimation methods are also available, such as dynamic conditional correlation [113] and the combination of variable parameter regression and Kalman filtering [114]. Regarding more conceptually novel metrics, dynamic time warping arguably better accounts for nonlinearity and time lag between brain region timecourses: matching is made between two regional timecourses, enabling differential alignment over time, and the final element of the optimal alignment path is taken as the metric of interest [109]. Two BOLD timecourses may also be viewed in 2D space, from which the gradient magnitude weighted by its phase consists in an FC alternative [115].

Although *K*-means clustering was originally applied to retrieve CS [13], several more sophisticated methodological developments have gradually blossomed: for instance, group information-guided ICA is a two-step procedure in which temporally overlapping, spatially independent connectivity patterns shared by the whole investigated subject population are first derived; in a second step, the dominant connectivity state of each subject is extracted with its associated timecourse [116]. In another work, a two-stage community detection approach was suggested to replace *K*-means clustering and directly estimate the optimal number of states [117]. An extensive comparison of metrics to infer the correct number of states has also recently been performed [118].

Finally, it is worth noting that, aside from the employed analytical pipeline, an adequate representation of the data is essential because a tensor-based description of whole-brain FC leads to different analytical outcomes compared to a vectorized simplification [119].

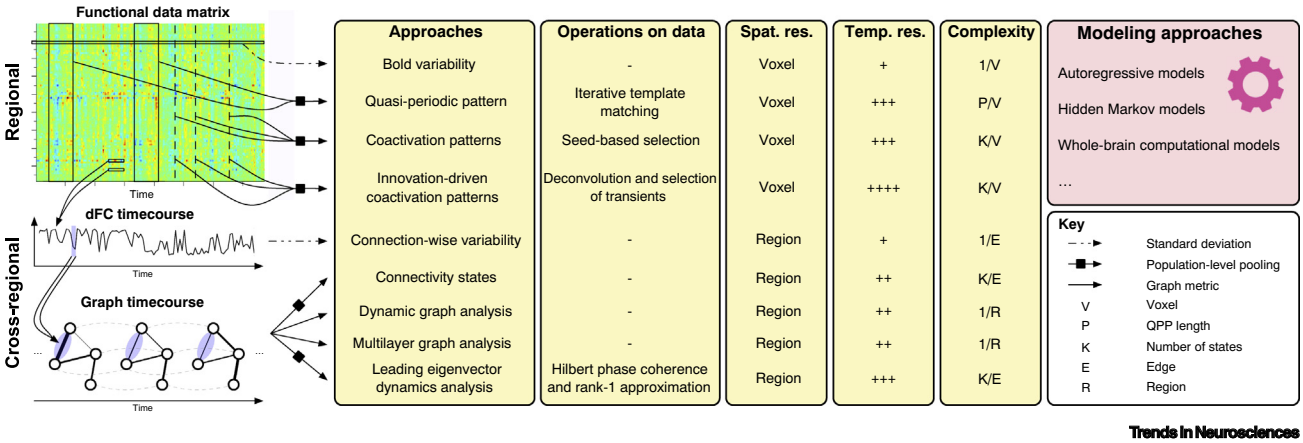

Figure 2. Conceptual Categorization of Dynamic fMRI Analytical Tools. Some dynamic analytical approaches extract regional activity features directly from the functional data matrix (top left), whereas others describe cross-regional relationships. This may be at the level of individual dynamic functional connectivity (dFC) timecourses (middle left) or at the whole-brain scale (bottom left), where one connection then stands as the edge of a graph (as annotated in light blue), changing in FC over time. Existing approaches are listed from top to bottom (first yellow box from the left) along this hierarchy. A dashed arrow reflects quantification of the standard deviation, a solid arrow denotes the computation of a graph metric (in this review, we primarily consider regional flexibility), and an arrow with an embedded rectangle means that data from separate subjects must be pooled to gather dynamic estimates. For multilayer graph analysis, additional edges are added to the graph representation, as depicted by dashed lines. Each methodology can be further categorized in terms of the operations that must be applied to the data beforehand, the spatial resolution at which it operates (voxel-wise or regional), the temporal resolution of obtained dynamic measures (ranging from +, denoting little ability to pinpoint changes in time, to ++++ in the most optimal case), and its complexity (number of values extracted per voxel, edge, or region). Compared to most methods, modeling approaches (pink box top right) enable a mathematical description of the dynamical system at hand, and by this means potentially address causal system properties. Abbreviations: BOLD, blood oxygenation level-dependent; QPP, quasi-periodic pattern; Spat. res., spatial resolution; Temp. res., temporal resolution.

resulting in cross-regional and cross-time edges [22]. At the framewise level, recurring spatio-temporal patterns of activity, the quasi-periodic patterns, can also be extracted [23].

Temporal modeling approaches have also been introduced to conduct principled framewise analyses. For instance, autoregressive models have been applied at a regional spatial resolution [24]: although only R^2 coefficients (where R is the number of brain regions) embed information regarding temporal changes in brain activity, the approximation is as good as with state-based approaches. **Hidden Markov models** (HMMs) have also been applied by extracting patterns of activation parameterized by their mean and covariance [25].

Dynamic Approaches Have Been Leveraged to Study Behavior

Analysis approaches focused on dFC have potential for application to all aspects of behavior. We provide a selective overview of studies using different dFC approaches to investigate behavior, as summarized in Table 1.

Executive function is central to the continuous processing of information, and understanding its underlying processes in the brain is therefore aided by using dynamic compared to static approaches, as demonstrated using autoregressive models [26]. Overall, executive function has mostly been associated with increased dFC. In one study, the average dFC along time within the dorsal attentional network and between the **default mode network** (DMN), cerebellar, and ventral attentional networks positively correlated with fluid intelligence [12]; in addition, CV within the DMN also positively correlated with executive function. Similarly, a comparison of meta-states between chess experts and beginners revealed that chess experts generally occupied more meta-states and exhibited more transitions between them [27]. In turn, both multilayer GA and dynamic GA showed that executive function was predicted by nodal flexibility, which describes the transition of nodes between different network configurations [28,29]. By contrast, sustained attention was enhanced by more stable connectivity in visual, motor, and executive-control networks at rest in a whole-brain CV analysis [30]. Furthermore, there is evidence for an interaction between emotional state and cognitive control: using a precuneus seed, a CAP associated with executive control networks was specific to cognitive control efforts after participants watched sad movie clips [31].

Recent research has also demonstrated a link between dFC and personality. In a state-based analysis focused on the DMN, salience, executive, and dorsal attention networks, openness to experience was stronger in subjects with longer dwell times in a state of overall positively correlated networks, perhaps because these interactions would support enhanced imagination and creativity [32]. In subjects with **major depressive disorder** (MDD), the temporal features of a connectivity state with strong within- and between-network connectivity of sensory-related networks were positively associated with extraversion, and negatively with neuroticism; both personality factors have been linked to MDD, potentially the reason why these associations were absent in healthy controls [33]. Another report focusing on interactions between subregions of the anterior insula and the rest of the brain found that subjects differentially occupy CS depending on their levels of empathy [34]. Importantly, to capture some aspects of personality there may be no added benefit of dynamic over static measures [26].

A more variable factor influencing behavior is psychological state, which has also been described with respect to changes in dFC. For instance, multilayer GA of several hours of longitudinal fMRI measures of one subject at rest revealed that increased subjective ratings of surprise and positive affect were related to respectively lower and higher nodal flexibility predominantly in the somatomotor network [35]. When considering multiple subjects, valence and arousal during

Table 1. dFC Studies Conducted to Study Human Behavior (in the Same Order as Reported in the Text)

Behavioral aspect	Analysis method	Ref
Executive control		
Executive function	Autoregressive models	[26]
Executive function	CV	[12]
Chess expertise	CS	[27]
Executive function	Dynamic GA	[28]
Executive function	Multilayer GA	[29]
Attentional control performance	CV	[30]
Cognitive control	CAPs	[31]
Personality		
Openness to experience	CS	[32]
Extraversion and neuroticism	CS	[33]
Empathy	CS	[34]
Personality	Autoregressive models	[26]
Psychological state		
Surprise and positive affect	Multilayer GA	[35]
Response to emotional speech (valence and arousal)	Inter-subject analysis	[36]
Emotional response to psychosocial stress	CS	[37]
Emotional response to sad stimuli	CAPs	[31]
Trait mindfulness		
Trait mindfulness	CS	[38]
Trait mindfulness	CS	[39]
Physiological state		
Sleep stages	CV	[42]
Sleep stages	HMM	[43]
Sleep deprivation	CS	[44]
Substance consumption		
Citalopram	CV	[45]
Nicotine absence in chronic smokers	CS	[46]
Psilocybin	LEiDA	[47]

listening to naturalistic speech stimuli predicted inter-subject phase synchronization of language and emotion circuits [36]. Furthermore, emotional responses following psychosocial stress have been associated with two unrelated CS: a positive and a negative emotion state comprising the ventromedial prefrontal cortex, amygdala, anterior insula, and anterior cingulate cortex [37]. Finally, a precuneus CAP including the DMN and anticorrelated elements within the anterior cingulate cortex and insula, resembling parts of the salience network, showed higher occurrences after subjects watched emotional compared with neutral movie clips [31].

Trait mindfulness has recently been studied as the stable tendency to have present-moment awareness. High trait-mindful young adults compared to low trait-mindful individuals transited more frequently towards a whole-brain connectivity state displaying strong anticorrelation between task-positive and task-negative networks, as well as large positive within-network correlation [38]. The authors of this study posit that this may be an energetically more costly state associated with refocusing. Meanwhile, in another analysis focused on dynamic interplays between the

DMN, sensory, and central executive networks in children and adolescents, more trait-mindful children were found to exhibit more frequent transitions across the derived CS, as well as a lower fraction of time spent in a state showcasing positively correlated DMN and central executive network [39].

In addition to describing psychological elements with dFC features, evidence has continued to accumulate regarding the impact of physiological state. Two reviews on the relationship between consciousness level and its neural correlates point towards reduced dFC with reduced level of consciousness [40,41]. An examination of the variance of regional dFC timecourses during sleep revealed that, in deeper sleep stages, CV was overall stronger, whereas the mean dFC value over time was lowered between distinct brain networks [42]. Thus, variability increases as consciousness diffuses. In addition, a study using an HMM at the spatial resolution of a regional atlas characterized 19 whole-brain states visited over the course of falling asleep, as well as their transitions, and thus expanded on the traditional understanding of sleep stages [43]. Another report using state-based analysis revealed a shift towards the expression of CS with reduced thalamocortical connectivity when participants were sleep-deprived. They also observed increased connectivity across cortical networks in a sleep-deprived state [44].

Substance consumption can also modulate functional brain dynamics because it alters physiological state. The effects of citalopram, a serotonin reuptake inhibitor, were assessed by computing CV between the medial prefrontal cortex and other DMN locations [45]: citalopram significantly lowered dFC variability with two clusters located in the posterior DMN, putatively because of reduced spontaneous mind-wandering. Similarly, in chronic smokers, abstinence was associated with fewer transitions between states, and complementary results from static analyses showed altered connectivity between insular subdivisions and three distributed networks (DMN, executive, and salience) [46]. Finally, using LEiDA, psilocybin (a serotonergic psychedelic) was shown to particularly suppress a state overlapping with the frontoparietal network [47].

Perturbed Dynamics in Autism Spectrum Disorder, Schizophrenia, and MDD

Psychiatric and neurodevelopmental disorders dramatically alter behavior at many levels, and this is reflected in changes in dFC. Reviews on the prediction of disorders from fMRI have discussed the use of dynamic techniques and found that models including dynamic measures typically outperform those relying on static measures [48,49]. Three disorders have been selected here to exemplify the clinical potential of characterizing individual behavioral variability using dFC approaches: **autism spectrum disorder** (ASD), schizophrenia, and MDD (summarized in Table 2). This selection reflects the relatively large amount of empirical work using dFC methods in these populations, but it also presents a complementary choice owing to the diversity of the disorders chosen [50,51].

ASD is an intensively studied neurodevelopmental condition that is associated with difficulties with social interaction, communication impairments, and repetitive behaviors. Recent reviews have touched upon the benefits of using dynamic analysis for understanding neurodevelopmental disorders, and have also highlighted a continued need for insights into dFC disruptions as a way to understand the neural underpinnings of ASD [52,53]. The evidence from both state-based and CV approaches points towards a pattern of hyperconnectivity and hypervariability in ASD. Specifically, but not exclusively, altered dFC in the DMN and salience network was reported [54–56]. Furthermore, differential expression of CS including thalamic–sensory connectivity was observed in ASD subjects aged on average 16 years [57]. Particularly interesting for clinical practice, inter-subject functional correlation was used to associate ASD symptomatology with the expression of CS during watching natural movies [58].

Table 2. dFC Studies Conducted to Study Brain Disorders Showcasing Behavioral Impairments (in the Same Order as Reported in the Text)

Brain disorder	Analysis method	Refs
Autism spectrum disorder		
ASD	CS	[54]
ASD	CV	[55]
ASD	CS	[56]
ASD	BOLD variability, CS	[57]
ASD	Inter-subject analysis	[58]
Schizophrenia		
Schizophrenia	CV	[59]
Schizophrenia	CV	[60]
Schizophrenia	CS	[61]
Clinical high risk of psychosis and early illness schizophrenia	CS	[62]
Schizophrenia	HMM	[63]
Schizophrenia	CV	[64]
Schizophrenia	Dynamic GA	[65]
Psychotic-like experiences	CS	[66]
First episode psychosis	Quasi-periodic patterns	[67]
High risk of psychosis	CAPs	[68]
Clinical high risk of psychosis and early illness schizophrenia	CS	[69]
22q11 deletion syndrome	iCAPs	[70]
Major depressive disorder		
MDD	CS	[33]
MDD	CS	[71]
MDD	CS, CV	[72]
MDD	Multilayer GA	[73]
First episode MDD, untreated	CS	[74]
MDD in remission	LEiDA	[75]

Schizophrenia, a debilitating mental disorder characterized by profound disruption of thinking, language, perception, and sense of self and reality, has continued to be a target of neuroimaging research. CV involving the left precuneus, a hub of both task-positive and task-negative networks, was stronger in schizophrenic patients relative to healthy controls, irrespective of genotype and treatment [59], whereas in another study, regional CV was increased in schizophrenia at the level of the somatomotor and visual networks, while a decrease was seen in the DMN and frontoparietal network [60]. At the level of CS, several studies found that schizophrenic subjects generally showed connectivity profiles of weak intra- and sometimes also reduced inter-network dFC compared with controls [61,62]. This pattern is consistent with reduced cognitive functioning. In line with these findings, results from an HMM formalism at the resolution of whole-brain networks evidenced an association between positive symptoms of schizophrenia and fractional occupancy in states with low activity in all networks, most prominently in the DMN and executive networks [63]. More focused analyses assessing the functional correlates of auditory hallucinations found that CV in schizophrenic subjects was reduced between the left auditory perception and speech-production brain areas [64].

When focusing on hallucination severity, a dynamic GA revealed that nodal flexibility of the lateral occipital cortex was perturbed in people with schizophrenia, and this was related to symptom strength [65].

Interestingly, dFC also shows functional specificities in subjects considered to be at risk of developing schizophrenia. Using dynamic conditional correlation, a framewise alternative to sliding window analysis (Box 2), a study showed that healthy subjects undergoing psychotic-like experiences spent more time in a state characterized by hypoconnectivity within the DMN, and hyperconnectivity within visual regions [66]. Moreover, measuring quasi-periodic patterns in participants with first-episode psychosis revealed hypoconnectivity in the frontoparietal network [67]. Similarly, a CAP analysis with an anterior insula seed demonstrated that individuals at high risk of psychosis have prolonged expression of a CAP that resembles the DMN, as well as decreased CAP switching, compared to healthy controls [68]. Furthermore, by extracting CS through group information-guided ICA, healthy controls, subjects at clinical high risk for psychosis, and early schizophrenia patients were shown to share a dominant state, but to differ in non-dominant states; notably, subjects at clinical high risk displayed altered connectivity patterns consistent with an intermediate stage between healthy and early illness schizophrenia patients [69]. In other work, iCAP analysis in patients with 22q11 deletion syndrome, a neurodevelopmental disease with a strongly elevated risk of schizophrenia, demonstrated that longer durations and couplings of iCAPs were associated with the severity of positive psychotic symptoms and anxiety, solidifying the case for a relationship between decreased dFC and schizophrenia [70].

Finally, MDD is one of the most prevalent psychiatric conditions, with great cost to individuals and society. Overall, patients with MDD present a pattern of hypoconnectivity; specifically, two state-based analyses revealed lower dwell times in connectivity states with strong within- and between-network connectivity regarding the auditory, somatosensory, and visual networks in patients [33,71]. This was supported by another state-based analysis centered on the DMN, salience, and executive networks: patients with MDD spent longer durations in a sparsely connected state [72]. In the same study, CV between the anterior DMN and right central executive network was found to be diminished. Similarly, a study using multilayer GA showed that nodal flexibility of the anterior cingulate cortex was impaired in MDD [73]. Conversely, a trend towards increased CV between the laterobasal amygdala nucleus and the supplementary motor area was found in untreated patients with first episode of MDD [74]. Finally, patients remitted from MDD show network abnormalities as seen with LEiDA, and these particularly include shorter duration and altered transitions in relationship to a state including the DMN, frontoparietal, and salience networks [75].

Concluding Remarks and Future Perspectives

We have examined the utility of a large range of time-resolved analytical approaches in capturing the dynamic features of fMRI data in studying different facets of behavior, and in shedding light on a select set of psychiatric and developmental disorders. Dynamic analytical approaches have been shown to provide benefits over static methods, particularly for behavioral aspects that are transient. In addition, we have also shown how these methodologies can be very useful in furthering our understanding of these disorders.

A first observation from this review is the current prominence of correlational dynamic approaches to probe brain function. Modeling frameworks that link fMRI measures to structural or molecular data [76,77] enable us to move closer to a causal understanding of brain dynamics (see Outstanding Questions). If the goal is to eventually act on behavior, rather than merely studying

Outstanding Questions

For which categories of behavior do dynamic methodologies to study fMRI signals contribute novel and meaningful information beyond that of their conventional static counterparts?

To what extent is the current understanding of behavior biased by the simplifying interpretations of most correlational approaches?

What is the most effective and thorough way to enable large-scale comparative analyses of behavior across different dynamic methodologies?

How is complex and adaptive behavior supported by interactions of large-scale functional brain networks?

How can one build system-level mechanistic brain models, integrating knowledge about brain function and structure, that are relevant for explaining and predicting behavior?

it (for example, by renormalizing brain activity in neural disorders), a model that can be perturbed is an essential tool [78].

A second observation stemming from this literature synthesis is that, although findings within the same behavioral aspect or disorder are somehow distinct from others, there is still considerable variance between studies and the areas implicated, and their dFC properties rarely overlap. Many factors may explain such discrepancies: first, small-sized subject populations with distinct demographic characteristics are generally studied, but dFC metrics are known to be particularly influenced by measurement noise or sampling variability, among other factors [79,80]. Data preprocessing choices or analytical settings (e.g., the number of considered CS) also often differ from case to case, as do acquisition parameters (for instance, the repetition time that dictates the best possible temporal resolution of the analyses). As touched upon in Box 1, some of these factors also relate to the amount of non-neural signal contributions in the analyses in a poorly understood manner. In addition, accurately studying an individual facet of behavior is in itself a daunting task because interplays manifest across several factors (e.g., physiological state may influence executive functions).

There are several ways to counter these problems: one is to take advantage of large-scale, publicly available datasets to address well-delineated research questions. Another promising option is the decentralization of dFC computations across physical locations, to foster cross-institutional analyses relying on similar (pre)processing choices [81]. In addition, it is also important to remain critical regarding existing approaches and their possible caveats: for example, if spatial dynamics exists on top of temporal dynamics, as recently argued [82], approaches relying on fixed atlas-based parcels would then be ill-posed by nature.

A final observation is that the breadth of explored behavioral aspects contrasts with the limited number of dynamic methods that are applied in practice. In most studies to date, CV or CS are computed (albeit almost never jointly, despite their reliance on the same sliding window framework), but there are many alternatives with potential to reveal complementary dynamic information owing to their conceptual specificities (e.g., faster-paced fluctuations with framewise investigations, or more localized subtleties with spatially focused techniques). In fact, the arsenal of existing dynamic methods far exceeds those discussed here (e.g., [83–85]). Because behavior is only contemplated from few methodological angles in relation to dynamics, our understanding of some of its facets may be biased.

As a solution, we believe that current efforts towards a more comparative investigation of dFC tools, which so far concern specific subfamilies of approaches [86–89], should be further pushed to a larger scale, complemented by attempts to more thoroughly mathematically characterize the relationships between different dynamic methodologies [90]. To this end, the increasing availability of publicly released tools to apply different families of dynamic approaches [91–94] is reassuring. In addition, a possibly fruitful way to encourage research laboratories to leverage their own methodologies towards such comparative insight may be via dedicated competitions (e.g., https://www.kaggle.com/c/trends-assessment-prediction/overview) or large-scale collaborative efforts that unite the methodological know-how from various experts in their respective techniques.

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