Colloquium: Multiscale modeling of brain network organization

Charley Presigny and Fabrizio De Vico Fallani[*]

Sorbonne Université, Institut du Cerveau—Paris
Brain Institute—ICM, CNRS, Inria, Inserm,
AP-HP, Hôpital de la Pitié Salpêtrière,
F-75013 Paris, France

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A complete understanding of the brain requires an integrated description of the numerous scales and levels of neural organization. This means studying the interplay of genes and synapses, but also the relation between the structure and dynamics of the whole brain, which ultimately leads to different types of behavior, from perception to action, while asleep or awake. Yet multiscale brain modeling is challenging, in part because of the difficulty to simultaneously access information from multiple scales and levels. While some insight has been gained on the role of specific microcircuits on the generation of macroscale brain activity, a comprehensive characterization of how changes occurring at one scale or level can have an impact on other ones remains poorly understood. Recent efforts to address this gap include the development of new frameworks originating mostly from network science and complex systems theory. These theoretical contributions provide a powerful framework to analyze and model interconnected systems exhibiting interactions within and between different layers of information. Recent advances for the characterization of the multiscale brain organization in terms of structure-function, oscillation frequencies, and temporal evolution are presented. Efforts are reviewed on the multilayer network properties underlying the physics of higher-order organization of neuronal assemblies, as well as on the identification of multimodal network-based biomarkers of brain pathologies such as Alzheimer's disease. This Colloquium concludes with a perspective discussion of how recent results from multilayer network theory, involving generative modeling, controllability, and machine learning, could be adopted to address new questions in modern physics and neuroscience.

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CONTENTS

I. INTRODUCTION

The brain is a formidable complex system exhibiting a wide repertoire of emergent phenomena, such as criticality, that ultimately rule the behavior of many living beings (Beggs and Plenz, 2003; de Arcangelis, Perrone-Capano, and Herrmann, 2006; Chialvo, 2010; Fontenele *et al.*, 2019; Wilting and Priesemann, 2019). These phenomena involve multiple spatial scales, from molecules to the whole brain, and stem from multiple temporal scales, from submilliseconds to the entire lifespan (Robinson *et al.*, 2005). More broadly, scales can refer to other types of dimensions or levels (Brooks, DiFrisco, and Wimsatt, 2021), such as complementary phenomenological information captured by different experimental technologies (such as magnetic resonance imaging, electrophysiology, and genetics) or neuronal interactions at multiple topological levels (Betzel and Bassett, 2017b; Bazinet *et al.*, 2021) (Fig. 1).

Disentangling such organizational complexity, and investigating how the relationships between the system's parts give rise to its collective behavior, is crucial to understanding basic neural functioning (Turkheimer *et al.*, 2021) and, eventually, curing brain diseases (Cutsuridis, 2019). Modeling multiscale brain organization is indeed one of the most important
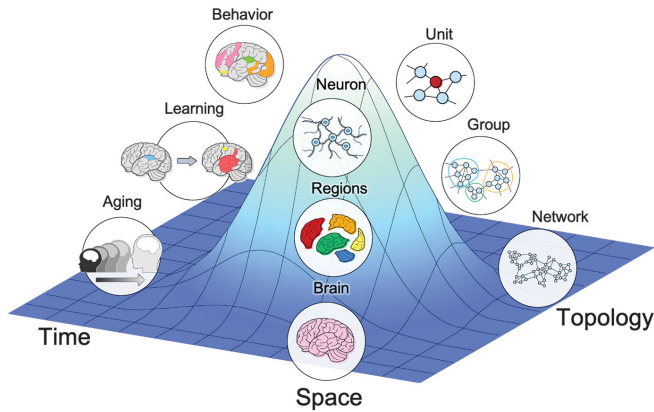
[*]fabrizio.de-vico-fallani@inria.fr

FIG. 1. Multiscale brain organization. The different organizational aspects of the brain system are represented over a multidimensional manifold. Three type of dimensions, or levels, are illustrated here, i.e., time, space, and topology. From the top to the bottom of the manifold, the scales of each organizational level go from micro to macro. From Thibault Rolland.

challenges of our century. The number of flagship initiatives funding large projects that aim to reproduce multiscale brain behavior has significantly increased in the last two decades; the Human Brain Project,[1] the Brain Initiative,[2] and the China Brain Project (Poo *et al.*, 2016) represent just a few examples.

While at present there is no comprehensive theory of how to bridge multiple scales and levels, the pursuit of such a theory remains critically important. Several recent models propose new ways to model neural activity within and between multiple scales, and further provide mechanistic insights into the structure and dynamics of brain organization. Hence, it is timely to discuss these emerging developments, and to seek to tie them together into a meaningful theoretical field that tackles current open questions in multiscale neuroscience and medicine from a system perspective.

Research in the field has progressively acknowledged the importance of considering brain organization from a holistic perspective and not from a reductionist angle (Deco, Jirsa, and McIntosh, 2011; Breakspear, 2017; Engel, Schlvinck, and Lewis, 2021). This is somewhat implicit in the term organization itself, which stems from the medieval Latin *organizatio*, i.e., the arrangement of parts in an organic whole. Accumulating evidence indicates that modeling how different brain components interact is often more realistic and effective in terms of behavior prediction than simply considering their activity in isolation (Scannell *et al.*, 1999; Friston, 2011).

Graphs or networks have progressively emerged as a natural way to describe heterogeneous connectivity diagrams at single scales or levels (Jouve, Rosenstiehl, and Imbert, 1998; Sporns, Tononi, and Edelman, 2000; Hilgetag and Kaiser, 2004; Stam and Reijneveld, 2007; Park and Friston, 2013). According to this framework, the nodes of a network correspond to different brain sites, such as neurons, neuronal ensembles, or even larger areas, but also to electric or optical sensors. The edges,

or links, of the network represent either anatomical (structural) connections or functional (dynamical) interactions between the nodes. While the best practices for establishing the links between brain nodes are still evolving, the type of connectivity basically depends on the experimental technology. Anatomical brain networks are often derived from postmortem tract tracing or *in vivo* or *in vitro* structural imaging [such as diffusion tensor imaging (DTI)] (Rubinov and Sporns, 2010). Dynamical brain networks are instead mostly obtained from *in vivo* and *in vitro* functional imaging, such as optical imaging, electrophysiology [electroencephalography (EEG), magnetoencephalography (MEG), etc.], or functional magnetic resonance imaging (fMRI) (De Vico Fallani *et al.*, 2014).

The use of a network formalism to study the structure and dynamics of interconnected brain systems has a rich and pervasive heritage in seminal works at the intersection between physics and neuroscience. Studies on single-scale brain networks produced major results and provided structure around concepts and languages inspired by statistical physics and complex systems theory. Like other real interconnected systems, brain networks tend to exhibit an optimal balance between integration and segregation within their connectivity structure (Bassett and Bullmore, 2017). This peculiar structure, also known as *small world*, is topologically characterized by the co-occurrence of short paths and abundant clustering links between nodes (Watts and Strogatz, 1998). Small-world networks ensure efficient communication between the nodes and favor global synchronization of oscillatory dynamics (Lago-Fernández *et al.*, 2000; Latora and Marchiori, 2001).

Brain networks also exhibit other important topological properties, such as mesoscale modular organization as well as the presence of core hubs passing information between peripheral distant brain areas (Bullmore and Sporns, 2009; Zamora-López, Zhou, and Kurths, 2010; van den Heuvel and Sporns, 2011; Markov *et al.*, 2013). In addition, being embedded in space, brain networks are economic as they tend to minimize the energetic cost (such as the metabolic cost) associated with the presence of long-range connections (Bullmore and Sporns, 2012).

At this stage it is important to remember that the brain is a flexible system and that its organization can adapt to the external environment, endogenous and exogenous inputs, as well as brain diseases or after damage. As a consequence, topological properties of brain networks can exhibit shifts from normative physiological values and those deviations constitute the basis for the identification of new organizational mechanisms and biomarkers in both cognitive and clinical neuroscience (Stam, 2014; Zalesky *et al.*, 2014; Fornito, Zalesky, and Breakspear, 2015; Medaglia, Lynall, and Bassett, 2015; Fornito, 2021).

All the aforementioned findings refer to brain networks obtained separately from different levels of information. Here we expand the link between physics and neuroscience by building a unifying framework to analyze and model neural organization across multiple scales and/or dimensions from a network perspective. Specifically, we focus on approaches based on multilayer network theory, a recent field connected to physics through nontrivial results related to structure, dynamics, criticality, and resilience (De Domenico *et al.*,

2013; Boccaletti *et al.*, 2014; Radicchi, 2014; Nicosia *et al.*, 2017; Aleta and Moreno, 2019; Della Rossa *et al.*, 2020; Danziger and Barabási, 2022).

In addition, network models based on hyperbolic geometry were recently introduced to reproduce brain networks at different coarse-grained spatial resolutions, providing new insights on brain self-similarity and criticality (Allard and Ángeles Serrano, 2020; Zheng *et al.*, 2020). More traditionally, multiscale brain modeling can be performed by designing biophysical models of single-scale dynamics and simulating simple interlayer connectivity schemes (Siettos and Starke, 2016; Lytton *et al.*, 2017; Cutsuridis, 2019). Interested readers should consult the previously mentioned references for more information about these alternative approaches.

The remainder of this Colloquium is organized as follows. In Sec. II, we illustrate the rationale of multiscale brain modeling and review the main research lines and challenges. These arguments allow the introduction of multilayer network theory to characterize brain network organization across multiple scales and levels. In Sec. III, we present the multilayer network formalism by providing basic notions and definitions. We then introduce ways of characterizing multilayer network properties that have been extended to network neuroscience. Section IV describes the different types of multilayer brain networks that have been investigated thus far. Emphasis is given to the relevance of multilayer modeling as compared to single-layer alternatives and to the current practices to infer them from experimental data. We next give in Sec. V a few examples showing how multilayer network theory has been used to characterize and understand brain structure and function in physiological conditions. In Sec. VI, we then describe which multilayer network properties deviate from normative values in the presence of brain diseases, and how to derive predictive biomarkers of network reorganization associated with clinical outcomes. We close in Sec. VII by outlining the emerging frontiers of multilayer network theory that can be developed to advance multiscale brain modeling. Except when otherwise stated, brain networks refer here to connectivity graphs obtained with neuroimaging techniques in humans. Nonetheless, the presented formalism is broadly relevant and applicable to other animal species (primates and nonprimates), data modalities (*in vitro* and *in vivo*), and simulated neural models (*in silico*).

By reviewing the research endeavors on multilayer network theory to study the brain, we aim to stimulate a discussion and reflection on the exciting opportunity that it constitutes for multiscale neural modeling. To this end, we keep jargon to a minimum and adopt an accessible language to reach the broadest possible multidisciplinary science community.

II. MULTISCALE BRAIN MODELING

The goal of multiscale modeling is to describe a system's behavior by simultaneously considering multiple features, or mechanisms, taking place and interacting on different levels of information. These levels may represent phenomena of different nature, such as in continuum mechanics and molecular dynamics, or at different spatiotemporal resolution, i.e., from microscale to macroscale. Multiscale modeling is therefore

central for an integrated understanding of a complex system and for a prediction of its emergent properties. Since most real-life phenomena involve a broad range of spatial or temporal scales, as well as the interaction between different processes, multiscale modeling has been widely adopted in several disciplines, ranging from material science and algorithmics to biology and engineering (Weinan, 2011).

In neuroscience, multiscale modeling has historically considered multiple levels ranging from microscopic single neuron activity to macroscopic behavior of collective dynamics. This is achieved by bridging biophysical mechanistic models of neuron dynamics and experimental neuroimaging data (Gerstner, Sprekeler, and Deco, 2012). This bottom-up approach allows one to predict macroscopic observables by integrating information at smaller scales, typically under the assumption of mean-field approximations (Breakspear and Stam, 2005; Siettos and Starke, 2016; Goldman *et al.*, 2019). This means that the neuronal ensembles' dynamics are progressively averaged across scales leading to a characteristic hierarchical nested structure where multiple units at finer-grained levels map onto a new entity at coarser-grained ones [Fig. 2(a)] (Freeman, 1975; Kozma and Freeman, 2003; Chialvo, 2010; Expert *et al.*, 2011).

The thalamocortical model is perhaps one of the simplest examples that can reproduce disparate physiological and pathological conditions, from Parkinson's disease to epileptic seizures (Lopes da Silva *et al.*, 1974; Jirsa and Haken, 1996; Sherman and Guillery, 1996; Bhattacharya, Coyle, and Maguire, 2011; Bonjean *et al.*, 2012; Sohanian Haghighi and Markazi, 2017). In this model, both basic microscopic neurophysiology (such as synaptic and dendritic dynamics) and mesoscale brain anatomy (such as corticocortical and corticothalamic pathways) are progressively incorporated to predict large-scale brain electrical activity [Fig. 2(b)].

With the advent of new technologies and tools that allow more precise experimental data and efficient processing to be gathered, multiscale brain modeling has witnessed a significant transformation in the last decade. Increasingly sophisticated and accurate models have been proposed, including large-scale anatomical and functional brain connectivity (Deco *et al.*, 2008; Deco, Jirsa, and McIntosh, 2011). However, for one to fully understand a multiscale system, models at different scales must be coupled together to produce integrated models across multiple levels. Indeed, global brain dynamics are strongly dependent on the interaction of several interconnected subnetworks that contribute differently to generate them. Thus, the study of how intrascale and interscale interactions give rise to collective behavior and to relationships with their environment is a central theme of modern multiscale brain modeling. Because of the substantial lack of biological evidence, especially concerning interscale connectivity, large parts of studies have focused on analytical and numerical approaches (Dada and Mendes, 2011). For example, intrascale interactions have been simulated adopting cellular automata perspectives (Kozma *et al.*, 2004), while interscale connectivity has been established using wavelet transformations (Breakspear and Stam, 2005).

The use of top-down approaches, which start with the observation of biological characteristics in the intact system and then construct theories that would explain the observed
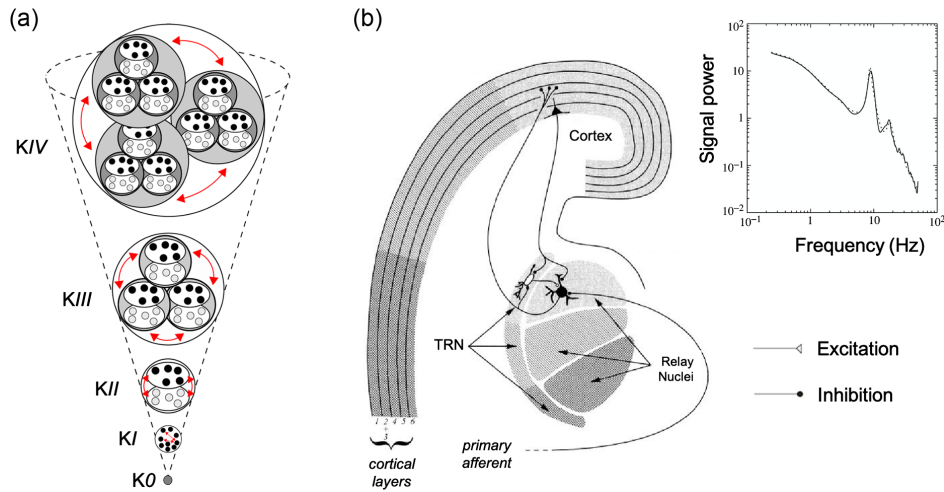
FIG. 2.   Bottom-up hierarchical modeling. (a) The so-called K-set hierarchy showing the model progression from cell level to entire brain. K0 is a noninteracting collection of neurons. KI corresponds to a cortical column with sufficient functional connection density. KII represents a collection of excitatory and inhibitory populations. KIII is formed by the interaction of several KII sets and simulates the known dynamics of sensory areas with $1/f$ spectra; see the inset in (b). KIV is formed by the interaction of three KIII sets that models the genesis of simple forms of intentional behaviors. Adapted from Kozma *et al.*, 2007. (b) Schematic view of major components involved in thalamocortical interactions. Different shading patterns code for different zones of the system, i.e., from micro [relay nuclei, thalamic reticular nuclei (TRN)] to macro scales (cortex). As indicated by the key, all connections shown are excitatory except for the connection from the reticular cell to the relay cell, which is inhibitory. Adapted from Sherman and Guillery, 1996. Inset from Robinson *et al.*, 2005.

behaviors, offers complementary solutions. In particular, data-driven methods based on statistical processing of neuroimaging data allow one to infer network representations of the brain at both anatomical and functional levels. Anatomical brain networks, also known as structural networks, are typically derived from 3D modeling techniques that identify nerve tracts using data collected by diffusion MRIs (Basser *et al.*, 2000). Functional brain networks, sometimes referred to as dynamical networks, are instead estimated by computing similarities between the activity signals generated in different brain sites. To this end, related measures such as Pearson correlation or Granger causality can be used, depending on the nature of the experiment and the type of scientific question (De Vico Fallani *et al.*, 2014). The use of cross-frequency coupling represents a promising approach to derive interscale interactions across multiple signal oscillation frequencies (Jirsa and Müller, 2013). Thus, while multiscale modeling in neuroscience has historically had a strong spatial connotation, it currently spans disparate levels of information, from structure and function to multiple oscillatory regimes and temporal evolution. Top-down approaches can therefore be used to generate richer and more realistic models reproducing real brain connectivity schemes and not just simulated ones (Siettos and Starke, 2016).

However, richer information and more accurate models also mean higher complexity and harder interpretation. These are both typical characteristics of multiscale problems that require the use of efficient algorithms to simulate the fully integrated model and appropriate ways of analyzing and interpreting them (Chi, 2016). This is one of the main challenges of large research projects supported by funding agencies around the world, such as the European Human Brain Project[3] and the

U.S. BRAIN Initiative.[4] The increasing number of open-source tools that can be freely accessed and customized to enrich multiscale brain models simply confirms how broad and multidisciplinary the community effort is (Hines and Carnevale, 2001; Eppler *et al.*, 2009; Sanz Leon *et al.*, 2013; Dura-Bernal *et al.*, 2019).

In all this turmoil, questions like the following appear to be essential for advancing multiscale models: how to model within-level and between-level relationships, how to characterize the resulting higher-order network properties, and what the critical phenomena emerging from the interaction of multiple levels are. These questions and associated notions motivate the construction of a theory that explicitly builds on the capability to simultaneously characterize intralayer and interlayer connectivity. In Sec. III, we introduce the methodological framework of multilayer network theory, which is at the basis of recent developments in multiscale modeling of neural functioning.

III. MULTILAYER NETWORK FORMALISM

A. Mathematical definition of multilayer networks

The need to investigate complex systems with multiple types of connectivity has emerged, almost independently, from different disciplines including social science, engineering, and computer science (Wasserman and Faust, 1994; Little, 2002; Dunlavy, Kolda, and Kegelmeyer, 2011). More recently the physics community also produced pioneering works on notions such as networks of networks (Zhou *et al.*, 2006, 2007), node-colored networks (Newman, 2003; Vazquez, 2006), interdependent networks (Buldyrev *et al.*,
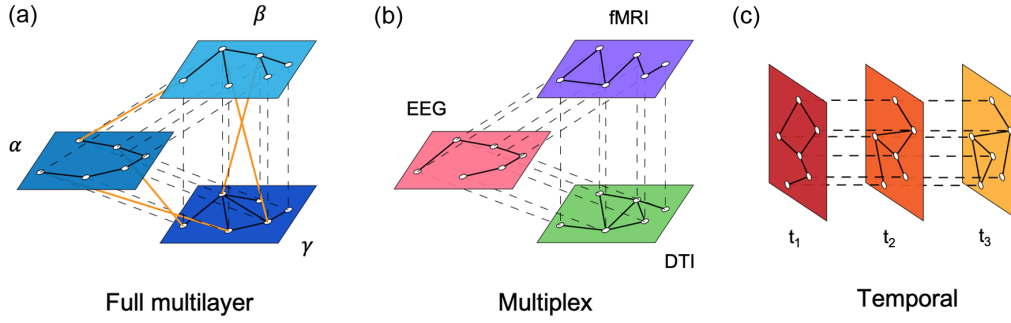

FIG. 3. Main configurations of multilayer networks. (a) Full multilayer network. Both within- and between-layer connections are allowed with no specific restrictions. This configuration is typically adopted to model multifrequency brain networks; see Sec. IV.A. (b) Multiplex network. Only interlayer connections between the replica nodes are allowed. There are no restrictions on connections within layers. This configuration is typically used to model multimodal brain networks; see Sec. IV.A. (c) Temporal network. Interlayer connections are allowed only between adjacent layers. There are no restrictions on connections within layers. This configuration is typically adopted to model time-varying brain networks; see Sec. IV.A. From Thibault Rolland.

2010; Gao *et al.*, 2012), and multilayer networks (Jo, Baek, and Moon, 2006; Kurant and Thiran, 2006). As a consequence, different terms have been introduced and adopted, thus producing a lack of a consensus set of terminology and mathematical formulation. Only in the last decade have we witnessed the dawning of general frameworks compatible with tools from complex systems and network science (Boccaletti *et al.*, 2014; Kivelä *et al.*, 2014), or based on tensorial formalisms (De Domenico, 2017).

Formally, a *multilayer network* is defined as $\mathcal{M} = (\mathcal{G}, \mathcal{C})$, where $\mathcal{G}$ is a set of graphs and $\mathcal{C}$ is a set of edges connecting the nodes of the different graphs (Boccaletti *et al.*, 2014). More precisely, $\mathcal{G} = \{G_\alpha | \alpha \in \mathbb{N}\}$, with $G_\alpha = (V_\alpha, E_\alpha)$ a graph at layer α. V_α is the set of nodes of G_α and E_α is the set of its edges, with $E_\alpha \subseteq V_\alpha \times V_\alpha$. The set of edges between the nodes of the graphs at different layers α and β is denoted by $\mathcal{C} = \{E_{\alpha\beta} \subseteq V_\alpha \times V_\beta | \alpha \neq \beta\}$.

An equivalent but less formal convenient representation of a multilayer network is given by the so-called supra-adjacency matrix $A = \{a_{ij}^{\alpha\beta}\}$. Here the element $a_{ij}^{\alpha\beta}$ represents the link between node i in layer α and node j in layer β. Hence, given M layers in the graph, A will result in a matrix with M blocks on the main diagonal, accounting for the connections within layers, and $M(M-1)$ off-diagonal blocks describing the links between different layers [Eq. (1)].

The previous definitions are general and allow one to describe complex systems exhibiting different numbers of nodes in each layer or scale, directed or undirected interactions, and weighted or unweighted connectivity. Based on state-of-the-art studies (Bianconi, 2018), we consider here multilayer networks composed of *replica* nodes. That means that all the layers will have the same number of nodes representing the same units of the system across different scales. Note that this is a specific condition that, however, matches the nature of data presented in a large segment of the studies conducted thus far. In this configuration $V_\alpha = V, \alpha \in \{1, \ldots, M\}$, and only connectivity within and between layers is allowed to change [Fig. 3(a)]. In the following, we refer to these general configurations as to *full multilayer* networks. The supra-adjacency matrix of full multilayer networks has the following form:

$$A = \begin{pmatrix} E_{11} & E_{12} & \ldots & E_{1M} \\ E_{21} & E_{22} & \ldots & E_{2M} \\ \vdots & \ddots & \vdots & \vdots \\ E_{M1} & E_{M2} & \ldots & E_{MM} \end{pmatrix}, \tag{1}$$

where $E_{\alpha\beta}$ contains interlayer links when $\alpha \neq \beta$ and intralayer links when $\alpha = \beta$.

Specific cases of full multilayer networks are the so-called multiplex networks. In multiplex networks, interlayer connections are not present, apart from those between replica nodes [Fig. 3(b)]. These links inform the model of the existing nodal correspondences across layers. Hence, in a multiplex $V_\alpha = V, \alpha \in \{1, \ldots, M\}$ and $\mathcal{C} = \{E_{\alpha\beta} \subseteq \{(v, v) | v \in V\} | \alpha \neq \beta\}$. The associated supra-adjacency matrix becomes

$$A = \begin{pmatrix} E_{11} & I & \ldots & I \\ I & E_{22} & \ldots & I \\ \vdots & \ddots & \vdots & \vdots \\ I & I & \ldots & E_{MM} \end{pmatrix}, \tag{2}$$

where I is the $N \times N$ identity matrix.

Based on the previous configurations, many types of multiscale interconnected systems (spatial, temporal, multimodal, etc.) can be represented and investigated. For example, *temporal* networks are represented by a particular type of multiplex, where only replica nodes between adjacent layers are interconnected, and the blocks after the first diagonals in Eq. (2) become zero matrices [Fig. 3(c)]. We notice that in general the information contained in multilayer networks can be obtained neither from equivalent aggregated versions (such as when links are averaged across layers) nor from standard network metrics and tools (Zanin, 2015). For this reason, it is crucial to derive new concepts and methods to quantify the higher-order topological properties emerging from multilayer networks. In Sec. III.B, we introduce some of the metrics and tools that have been developed thus far, as well as those that have been adopted in neuroscience. For simplicity, we focus

here on unweighted and undirected multilayer networks. For a more complete picture of multilayer network theory, see the reviews by Boccaletti *et al.* (2014) and Bianconi (2018).

B. Analytical tools for multilayer networks

In the following, we present some of the multilayer methods that have been used most frequently in neuroscience. We categorize them according to the topological scale that they characterize, i.e., from nodes (microscale) to the entire network (macroscale) passing by groups of nodes (mesoscale). Remember that the entry $a_{ij}^{\alpha\beta} = a_{ji}^{\alpha\beta}$ of the supra-adjacency matrix A describes the interaction of node i in layer α to node j in layer β of a given multilayer network. Since A is binary, $a_{ij}^{\alpha\beta}$ has a value of either 1 (presence of a link) or 0 (absence of a link). Note that a_{ij}^{α} represents intralayer interactions in layer α. For simplicity, we do not consider here self-loops, i.e., $a_{ii}^{\alpha} = 0$. Finally, we denote the number of layers as M and the number of replica nodes in each layer as N.

1. Microscale topology

The most intuitive nodal metric in classical network theory is the *node degree*, which measures the actual number of links that a node shares with the others. The equivalent measure in multiplex networks is the so-called overlapping degree or strength o_i, which simply sums the weighted degrees of node i across all layers.

Another popular metric for measuring how the degrees of node i are arranged across all layers is the multiplex participation coefficient (Battiston, Nicosia, and Latora, 2014):

$$p_i = \frac{M}{M-1}\left[1 - \sum_{\alpha}^{M}\left(\frac{k_i^{\alpha}}{o_i}\right)^2\right], \quad (3)$$

where k_i^{α} is the degree of node i at layer α. When $p_i = 0$, the links of the node are concentrated in one layer; when $p_i = 1$, they are uniformly distributed across layers.

Triads of interconnected nodes, also called *triangles*, are simple configurations supporting transitivity, clustering, and information segregation in the network (Newman, 2010). Locally, this tendency is quantified via the clustering coefficient, which measures the proportion of nodes linked to a given node that are also linked together (Watts and Strogatz, 1998). A relatively straightforward extension is the multiplex clustering coefficient (Cozzo *et al.*, 2015)

$$c_i = \frac{\sum_{\alpha}\sum_{\beta \neq \alpha}\sum_{j \neq i, m \neq i} a_{ij}^{\alpha} a_{jm}^{\beta} a_{mi}^{\alpha}}{(M-1)\sum_{\alpha}\sum_{j \neq i, m \neq i} a_{ij}^{\alpha} a_{mi}^{\alpha}}, \quad (4)$$

which takes into account the possibility of forming triangles by means of links belonging to two different layers.

These metrics determine which nodes are the most *central* in the network. In general there are many ways of defining the centrality of a node. For example, based on the computation of the shortest paths, the *betweenness* of a node measures its tendency to topologically connect distant parts of the network (Freeman, 1977). The extension to multiplex networks is the so-called overlapping betweenness centrality, which reads (Yu *et al.*, 2017a)

$$b_i = \frac{1}{(N-1)(N-2)}\sum_{\alpha}\sum_{s, s \neq t}\sum_{t, t \neq i}\frac{\sigma_{st}^{\alpha}(i)}{\sigma_{st}^{\alpha}}, \quad (5)$$

where $\sigma_{st}^{\alpha}(i)$ is the number of shortest paths from nodes s to t passing through node i in layer α and σ_{st}^{α} is the total number of shortest paths between nodes s and t in layer α.

Another well-known centrality measure is the PageRank centrality, which was initially used in Google Web search engines (Brin and Page, 1998). PageRank centrality can be thought of as roughly the fraction of time a random walker spends visiting a node traveling through the links of the network. In multiplex networks, random walkers have the possibility of jumping to adjacent nodes and teleporting to nodes in other layers, according to a modified version of the transition probability; see Halu *et al.* (2013) and De Domenico, Solé-Ribalta *et al.* (2015) for more details.

2. Mesoscale topology

Network *motifs* are recurrent connection patterns involving few nodes, which makes them easily interpretable. They constitute the basic building blocks of a complex system architecture coding for essential biological functions such as autoregulation, cascades, and feed-forward loops (Milo *et al.*, 2002; Sporns and Kötter, 2004; De Vico Fallani, Latora *et al.*, 2008).

When dealing with multiplex networks, motifs can be formed by edges belonging to different layers (Battiston *et al.*, 2017). Hence, the total number of possible configurations depends not only on the number of layers but also on the type of interaction, negative or positive. In these cases, Z scores are typically used to determine the statistical abundance of a multiplex motif G according to the following formula:

$$Z(G) = \frac{F(G) - \bar{F}_R(G)}{S_R(G)}, \quad (6)$$

where F is the occurrence frequency of a given multiplex motif, while $\bar{F}_R(G)$ and $S_R(G)$ are, respectively, the mean frequency and its standard deviation obtained from a set of equivalent random multiplex graphs R. Alternatively, frequency coherent subgraphs can also be extracted by counting their abundance in a set of multiplex brain networks corresponding to different individuals (Huang *et al.*, 2020).

The tendency of a network to form distinct groups, or clusters, of many nodes is an important prerequisite for the modularity of the system and its ability to process information in a segregated manner (Fortunato, 2010). The detection of these groups, which are also known as communities, is nontrivial, as one has to find an optimal separation that maximizes the number of links within groups and minimizes the between-group connection density (Newman, 2006).

In the case of multiplex networks, the definition of modularity incorporates the relation between different layers and partitions all the layers simultaneously (Mucha *et al.*, 2010):

$$Q = \frac{1}{2l}\sum_{ij\alpha\beta}\left[\left(a_{ij}^{\alpha} - \gamma_{\alpha}\frac{k_i^{\alpha}k_j^{\alpha}}{2l^{\alpha}}\right)\delta_{\alpha\beta} + \delta_{ij}H_{ij\beta}\right](\delta_{g_{i\alpha}, g_{j\beta}}), \quad (7)$$

where l is the total number of links in the multilayer, γ_α sets the granularity of the community structure in each layer, l^α is the total number of edges in layer α, $H_{ij\beta}$ is a parameter that tunes the consistency of communities across layers, and $\delta_{g_{i\alpha},g_{j\beta}} = 1$ when node i in layer α and node j in layer β belong to the same community, and 0 otherwise. Maximization of Q is finally obtained via heuristic methods and gives an optimal network partition for each layer (Blondel *et al.*, 2008).

In temporal networks, nodal metrics reflecting mesoscale network properties can be defined by measuring, for example, the *node flexibility*, i.e., the average number of times that a node changes community assignment across layers (Bassett *et al.*, 2011). A peculiar network partition consists of separating the network in a *core* of tightly connected nodes, and a *periphery* made by the remaining weakly connected nodes Borgatti and Everett (2000). As in a *rich club* (Colizza *et al.*, 2006), the presence of a core is crucial for the efficient integration of information between remote parts of the network (Csermely *et al.*, 2013; Rombach *et al.*, 2014; Zhang, Martin, and Newman, 2015; Verma *et al.*, 2016).

Battiston *et al.* (2018) introduced a fast core-periphery detection algorithm for multiplex networks. Based on local information (Ma and Mondragón, 2015), the method first defines a multiplex richness of a node by combining its degrees in each layer. Nodes are then ranked according to their multiplex richness values, and the core-periphery separation is given by the following optimal rank (Gonzalez-Astudillo *et al.*, 2021):

$$r^* = \arg\max(\mu_r^+)_r, \qquad (8)$$

where μ_r^+ is the richness obtained when one considers only the links of the node ranked in position r toward nodes with higher ranks. In the case of weighted multiplexes, the *coreness* of a node is given by the number of times that it belongs to the core after filtering the network with a range of different threshold values.

3. Macroscale topology

Large-scale properties of complex networks are often derived by aggregating information at smaller topological scales. For example, the global efficiency of a network, which is derived from the length of its shortest paths, quantifies the ability to integrate information from topologically distant nodes by means of a scalar number (Latora and Marchiori, 2001). In a multiplex network, a straightforward extension consists of computing the shortest paths across layers.

Based on topological distances, one can also quantify the global tendency of a multiplex network to form highly clustered and efficient groups as follows via the overlapping local efficiency (Latora and Marchiori, 2001; Yu *et al.*, 2017b):

$$E_{\text{loc}} = \frac{1}{N(N-1)} \sum_\alpha \sum_{i, i \neq j \in G_i} \frac{1}{k_i^\alpha(k_i^\alpha - 1)} \frac{1}{d^\alpha(i,j)}, \qquad (9)$$

where G_i is a subgraph containing the neighbors of node i and $d^\alpha(i,j)$ is the length of the shortest path between nodes i and j at layer α.

Tang *et al.* (2010) extended the concept of topological distance to temporal networks by introducing the characteristic temporal path length L, which measures the formation of shortest paths across consecutive layers. They also introduced a metric to quantify the probability that the neighbor set of a node that is present at time t is also present at time $t+1$. By averaging over all the nodes, they eventually defined the temporal-correlation coefficient C as

$$C = \frac{1}{N(M-1)} \sum_{i=1}^{N} \sum_{t=1}^{M-1} \frac{\sum_j a_{ij}^t a_{ij}^{t+1}}{\sqrt{(\sum_j a_{ij}^t)(\sum_j a_{ij}^{t+1})}}. \qquad (10)$$

Together the last two global metrics measure how the system information is, respectively, integrated and segregated over time and can be used to assess the small-world properties of time-varying networks (Tang *et al.*, 2010).

In graph theory, the Laplacian matrix has many useful implications in real networks, from denoising to low-dimensional embedding (Merris, 1994). The second smallest eigenvalue of the Laplacian, also called algebraic connectivity (λ_2), plays an important role since it informs several important properties of a network, such as community structure, synchronization, diffusion, and resilience (Fortunato, 2010).

In a full multilayer network, λ_2 is calculated from the associated supra-Laplacian matrix, whose elements are defined as

$$\mathcal{L}_{ij}^{\alpha\beta} = \begin{cases} \mu_i^\alpha, & \text{if } i = j, \alpha = \beta, \\ -a_{ij}^{\alpha\beta}, & \text{otherwise,} \end{cases} \qquad (11)$$

where μ_i^α is the total number of links (from any layer) incoming to node i at layer α.

In multilayer networks, λ_2 is sensitive to the amount of intralayer and interlayer connectivity and typically quantifies the integration-segregation balance among layers from a dynamical perspective (Gómez *et al.*, 2013; Radicchi and Arenas, 2013). λ_2 exhibits a phase transition when the interlayer connection intensity is increased from layers being independent and segregated to a high overall dependence and integration (Radicchi and Arenas, 2013).

IV. MULTILAYER BRAIN NETWORKS

A. Common types of multilayer brain networks

Up-to-date multilayer brain networks have been derived mostly from experimental neuroimaging data in humans, with nodes representing the same entities, i.e., brain areas across layers (Vaiana and Muldoon, 2020). Multiplex networks represent the easiest way to bridge brain connectivity at different levels, as one does not have to explicitly infer interlayer connections. In this situation, interlayer links connect the replica nodes only virtually and the associated meaning is basically the one of identity between the same nodes across layers [Fig. 3(b)] (Battiston, Nicosia, and Latora, 2014).

This type of representation has been used largely to describe multimodal brain networks, whose various layers may contain structural and functional connectivity (Simas

et al., 2015; Battiston *et al.*, 2018; Lim *et al.*, 2019), as well as interactions at different signal frequencies (De Domenico, Sasai, and Arenas, 2016; Guillon *et al.*, 2017; Yu *et al.*, 2017a). A common situation with multimodal networks is that the nodes might not correspond to the same entity in their native space. This is the case for brain networks derived from fMRI and EEG signals, where nodes correspond to image voxels and scalp sensors, respectively. To overcome this issue, advanced image and signal processing tools are used beforehand for projecting the native signals into the nodes of a common anatomical brain space, typically extracted from the structural MRIs of a subject's head (Baillet, Mosher, and Leahy, 2001; Michel *et al.*, 2004; Grech *et al.*, 2008). Multiplex networks have also been adopted to describe temporal brain networks, i.e., networks whose topology is changing over time (Bassett *et al.*, 2011; Braun *et al.*, 2015; Pedersen *et al.*, 2018). In this case, each layer corresponds to a specific point (or instance) in time, and only the replica nodes of temporally adjacent layers are interconnected according to a Markovian rule [Fig. 3(c)]. Unlike multimodal brain networks, the layers of a time-varying brain network do not correspond to different spatial or temporal-frequency scales, but they typically capture the dynamic network evolution within a fixed time resolution. This is typically of the order of milliseconds for motor behavior, minutes to hours for human learning, or years for aging as well as for neurodegenerative diseases.

Full multilayer network representations, containing both intralayer and interlayer nontrivial connectivity, have been adopted mostly to characterize brain signal interactions within and between different oscillation frequencies [Fig. 3(a)] (Tewarie *et al.*, 2016, 2021; Buldú and Porter, 2018). This representation is particularly useful for functional brain networks with a broad frequency content, such as in those obtained from electrophysiology, EEG, or MEG signals. Although less frequent than multiplex networks, this type of representation has great potential for characterizing whole brain cross-frequency coupling, which was recently shown to be crucial for many cognitive and pathological mental states (Jirsa and Müller, 2013).

Finally, we stress that, regardless of the type of construction, the resulting multilayer networks (either multiplex or full) generally exhibit higher-order properties that cannot be captured or resumed by simply aggregating information from different layers (Boccaletti *et al.*, 2014; Kivelä *et al.*, 2014).

B. Multilayer brain networks are more than the sum of their layers

Multilayer networks give richer descriptions than standard network approaches, but do they really represent a step forward into the modeling of brain organization? Why is aggregating layers not enough? Are all layers necessary to capture the main organizational properties? De Domenico, Nicosia *et al.* (2015) addressed these questions by introducing a *structural reducibility* approach to maximize the quantity of nonredundant topological information between the layers of a multiplex network with respect to its aggregated counterpart [Fig. 4(a)]. For a large spectrum of networks, from protein-protein interactions to social networks, structural reducibility showed that the best configuration in terms of
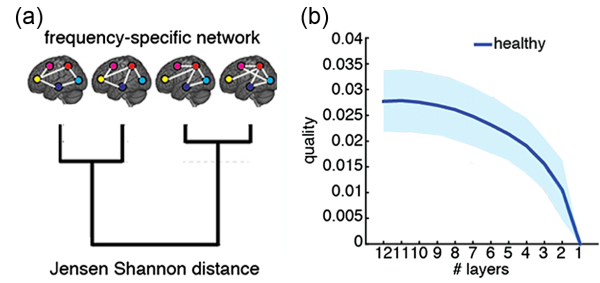

FIG. 4. Structural reducibility of multifrequency brain networks. (a) For each combination of layers a quality function measures the amount of new information added with respect to an equivalent single-layer model. (b) Median values of a quality function obtained from fMRI multifrequency brain networks in healthy subjects. Shaded areas indicate the standard deviation around each value. Adapted from De Domenico, Sasai, and Arenas, 2016.

distinguishability is not necessarily the one with the highest number of layers (De Domenico, Nicosia *et al.*, 2015). On the contrary, De Domenico, Sasai, and Arenas (2016) showed that multifrequency brain networks derived from fMRI signals were not easily reducible since all the layers brought some nonredundant topological information [Fig. 4(b)]. This result implies that even if fMRI oscillations are underrepresented at higher frequencies, their broad interaction remains crucial for correct brain functioning. We later show that this result extends generally and can be used to better diagnose brain diseases; see Secs. V and VI.

While most research has focused on multiplex brain networks, a better understanding of the emerging properties in full multilayer brain networks still remains to be elucidated. Buldú and Porter (2018) addressed these aspects by studying the difference between frequency-based multiplexes and full multilayers derived from MEG brain signals [Fig. 5(a)]. By evaluating the algebraic connectivity λ_2 (see Sec. III.B), they showed that full multilayer brain networks are close to the optimal transition point between the integration and segregation of the layers. The layers in the equivalent multiplex
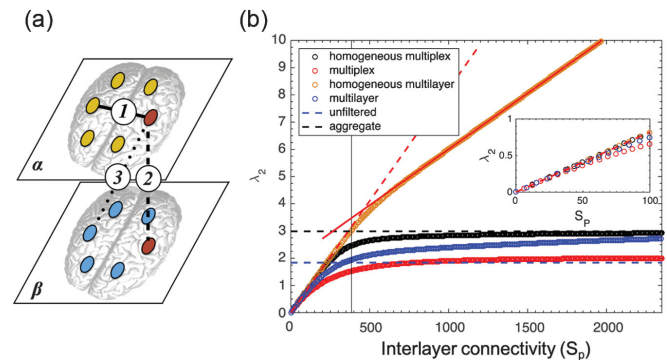

FIG. 5. Emergent properties in full multilayer brain networks. (a) Intralayer and interlayer edges in the multifrequency MEG network. 1-edge between regions at the same frequency. 2-edge of the same area between different frequency bands. 3-edge between different nodes at different frequency bands. (b) Algebraic connectivity λ_2 as a function of the total interlayer connectivity (S_p). The vertical solid line corresponds to the actual value of the interlayer connectivity, i.e., without modifying their weights. Adapted from Buldú and Porter, 2018.

configurations were instead more segregated and then far from this transition point (Radicchi and Arenas, 2013). These results were also confirmed by extensive numerical simulations and explained using the intrinsic lower interlayer connection density of the multiplexes [Fig. 5(b)]. The full multilayer λ_2 values were associated with the phase-amplitude coupling of gamma (30–40 Hz) and theta (4–7 Hz) brain frequency bands, confirming the crucial role of cross-frequency coupling in the study of complex brain function and dysfunction (Canolty *et al.*, 2006; Aru *et al.*, 2015). These findings indicate the importance of considering previously unappreciated cross-layer interactions to explain the emergent properties of brain organization.

C. Filtering spurious links in multilayer brain networks

Remember that brain connectivity networks are estimated from experimental data. This necessarily implies the presence of spurious connections, often among the weakest ones, due to the statistical uncertainty associated with the connectivity estimator and/or due to the presence of signal artifacts during the experiment (De Vico Fallani *et al.*, 2014; Korhonen, Zanin, and Papo, 2021). For example, head motions are known to abnormally increase short-range connectivity, thus altering the original topology of the network as well as its connection intensity, i.e., the sum of the actual links' weights (Lydon-Staley *et al.*, 2019). This is particularly relevant, as the topological properties of a network strongly depend on the number and weights of the existing edges (De Vico Fallani, Latora, and Chavez, 2017; Mandke *et al.*, 2018). As a result of the construction process, multilayer brain networks are also influenced by such noise, which might alter the true association between the multiscale brain network organizational properties and the subject's characteristics and behavior.

To mitigate the presence of unwanted alterations in the estimated links, two main strategies have been adopted to date following what has been done in standard network analysis. The first approach consists of manipulating the brain signals, while the second one operates directly on the connectivity matrices. Lydon-Staley *et al.* (2019) used the first approach to silence the effects of head motion on recorded brain signals and in turn on the estimated brain network. They tested different signal denoising strategies, based mainly on regression and source separation techniques (Cichocki and Shun-ichi, 2002) on temporal brain multiplexes constructed from fMRI data. Specifically, they evaluated their ability to attenuate the nuisance effects on several network metrics, such as multiplex modularity and node flexibility; see Sec. III.B. Despite some variability, the obtained results suggested that regression-based approaches outperform source separation–based techniques, possibly due to their ability to explicitly incorporate the nuisance variables in the denoising process (Lydon-Staley *et al.*, 2019).

The second approach consists of filtering the network's links. This is typically achieved by fixing a threshold either on the percentage of strongest edges to retain or on their weights. Depending on the threshold value, the resulting networks may have different densities and/or intensities. Mandke *et al.* (2018) evaluated the impact of network filtering on several topological properties, such as multiplex PageRank (see

Sec. III.B), multiplex modularity [Eq. (7)], and participation coefficient [Eq. (3)]. Specifically, they tested several filtering criteria, minimum spanning tree (MST) (Kruskal, 1956), efficiency cost optimization (ECO) (De Vico Fallani, Latora, and Chavez, 2017), and singular value decomposition (SVD) (Golub and Van Loan, 2012) applied to each single layer separately, or adapted to the entire multiplex.

When both synthetic and neuroimaging-derived multiplex networks were used, results indicated that SVD techniques lead to multilayer network properties that are robust to changes in connection density or intensity. MST and ECO techniques were instead effective only when each layer was separately filtered, and therefore useful when dealing with multimodal brain networks, where layers are estimated from different types of data and the nature of the interlayer links cannot be straightforwardly established. Note, however, that these results were obtained for multiplexes, and the extension to full multilayer networks remains to be investigated.

V. MULTILAYER NETWORK PROPERTIES OF BRAIN ORGANIZATION

A. Structure-function relationship

Both structural and functional brain organization are crucial determinants of complex neural phenomena such as cognition, perception, and consciousness (Park and Friston, 2013). An important question in modern neuroscience is how structural and functional connectivity are related to each other, and how such putative interactions can better our understanding of brain organization. Recent studies using both model-based and data-driven approaches have demonstrated that connectivity at the functional level could be predicted in part by the structural one, and that this prediction could explain several complex dynamics of brain functioning, from resting states to task-based and pathological conditions (Park and Friston, 2013; Hansen *et al.*, 2015; Surez *et al.*, 2020; Wein *et al.*, 2021).

But what are the higher-order topological properties of the multilayer network composed of both structural and functional layers and how do they help describe brain anatomofunctional organization? To address these questions, Battiston *et al.* (2017) first investigated the presence of simple connection motifs (see Sec. III.B) forming across the layers of a DTI-fMRI multiplex network. They found that motifs comprising both structural and positively correlated functional links are overabundant in the human brain [Fig. 6(a)]. This confirms that the presence of an anatomical connection is likely to induce a synchronized activity between the corresponding brain regions (Skudlarski *et al.*, 2008). However, other significant configurations were reported, including the presence of triangles in the functional layer with no support in the structural one. Overall, these results indicated that intrinsic functional organization of the brain is nontrivially constrained by the underlying anatomical network (Skudlarski *et al.*, 2008) and cannot be explained solely by it.

Ashourvan *et al.* (2019) later investigated the multilayer modularity of DTI-fMRI multiplex networks. The main results showed that the structural layer mostly dominates the community structure of the multiplex over a broad range of topological scales explored by varying the granularity
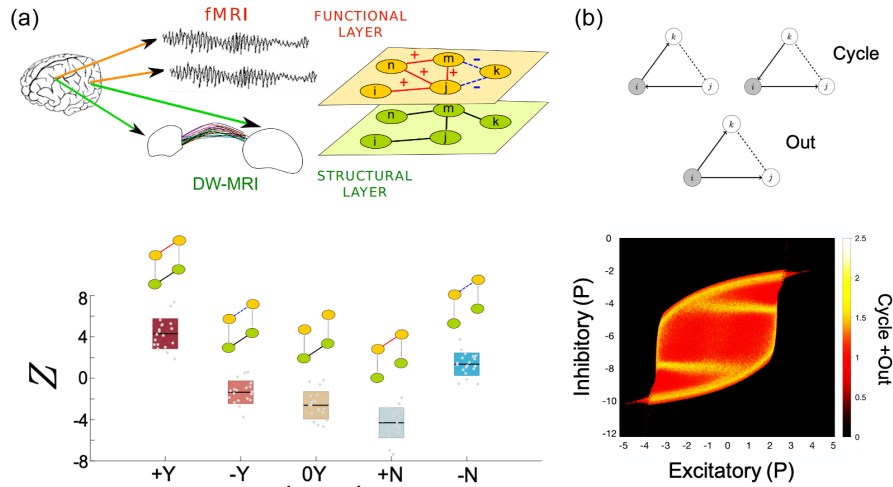
FIG. 6. Multiplex motif analysis of multimodal brain networks. (a) Structural-functional two-layer brain network. Interlayer links between replica nodes are omitted for visibility. Five nontrivial multiplex motifs of two nodes are possible based on the type of connectivity in the DTI structural layer [green (upper-layer) nodes] and in the fMRI functional layer [yellow (lower-layer) nodes]. The Z scores show the motifs that are overrepresented and underrepresented compared to equivalent random networks. Adapted from Battiston *et al.*, 2017. (b) Patterns of multiplex triangles comprising directed structural tuples (solid connections) closed by a functional edge (dashed connections). The overall motif counts normalized by equivalent random multiplexes are illustrated as a function of the basal activation parameters P and Q of the Wilson-Cowan model. Adapted from Crofts, Forrester, and O'Dea, 2016.

parameter γ [Eq. (7)]. The communities of the structural layer tended to spatially overlap with the cytoarchitectonic brain organization and were highly consistent among individuals. Instead, the communities of the functional layer were more heterogeneously distributed and less consistent across subjects, reflecting the dynamic repertoire of the brain functions (Ghosh *et al.*, 2008; Hadriche *et al.*, 2013).

By looking at DTI-fMRI multiplex networks, Lim *et al.* (2019) measured to what extent nodes with similar overlapping degrees tended to "wire" together, a property often referred as to assortativity. The results indicated that multimodal brain networks have a propensity to be assortative, which translates into an overall ability to facilitate system dynamics and resilience to random attacks (such as node removal) (Boccaletti *et al.*, 2014). This evidence resolved the assortative-disassortative dichotomy previously observed in a single-layer analysis of structural-functional brain networks. This multilayer assortativity resulted from a nontrivial structure-function interplay and indicated a novel organizational mechanism optimally balancing the resilience to damages and restrainability of their effects.

Modeling the emergence of large-scale brain dynamics from microscale neuronal interactions is crucial for a mechanistic understanding of neural multiscale organization. An early study by Zhou *et al.* (2007) proposed a computational model based on the structural connectome of the cat cortex. By parametrizing the coupling between several FitzHugh-Nagumo oscillators according to the available connectome, they simulated the ongoing activity in each region and estimated the interareal functional connections via Pearson's correlation (FitzHugh, 1961). By means of this simple model, Zhou *et al.* showed that a weak coupling parameter was sufficient to generate biologically plausible macroscale activity, with functional connectivity patterns mostly overlapping the modular organization of the structural network.

Crofts, Forrester, and O'Dea (2016) used a similar approach based on the structural connectome of a macaque cortex and Wilson-Cowan neuronal models (Wilson and Cowan, 1972). Of more relevance to this Colloquium, they analyzed the behavior of multiplex clustering patterns [such as in Eq. (4)] in the structural-functional networks as a function of two model parameters, i.e., one tuning the input to excitatory neurons and the other modulating the input to the inhibitory ones. Specifically, they defined multiplex clustering indices to quantify the presence of functional links associated with common drivers in the structural layer. The main results showed that such quantities were maximal at the boundaries of the phase transition, from steady-state to oscillatory dynamics, as well as in other regions of the parameter space [Fig. 6(b)]. Unlike previous results on single-layer analysis, this nontrivial behavior suggested that the system criticality depends not only on the structure-function interplay of the brain network but also on the type of ongoing dynamics.

On the level of a single neuron, Bentley *et al.* (2016) proposed a multiplex approach to represent synaptic connections (structural) as well as extrasynaptic signaling interactions (functional) inferred from gene expression data of the *C. elegans* worm. Despite the low degree of overlap between the synaptic and extrasynaptic connectomes, they found highly significant multiplex motifs (similar to those in Sec. III.B), pinpointing locations in the network where aminergic and neuropeptide signaling modulate synaptic activity. The presence of directed monoamine interactions and reciprocal synaptic connections was particularly significant among specific neurons implicated in learning, memory, and motor functions. These results support the evidence that the structural-functional interplay is crucial to better understanding the communication pathways between different parts of the *C. elegans* nervous system.

Along these lines, Maertens *et al.* (2021) identified the shortest paths from touch sensory neurons to motor neurons

allowing information flowing across different types of neurotransmitters and neuropeptide layers. By applying a time-delayed feedback control on the identified neurons, they could eventually reproduce the typical *C. elegans* locomotion and characterize the neuromuscular multilayer connectivity mechanisms associated with the central pattern generator (Gjorgjieva, Biron, and Haspel, 2014; Fouad *et al.*, 2018).

Multilayer network theory has just started to provide new tools and insight into the complex interplay of brain structure and function. Several issues remain to be explored, such as how to establish interlayer connections (Tewarie *et al.*, 2021) or incorporate multilayer network mechanisms in the laws modeling large-scale neuronal dynamics (Hansen *et al.*, 2015).

B. Information segregation and integration

Clustering and shortest paths are general concepts in complex systems that are both essential for the efficient organization of many real-world networks (Watts and Strogatz, 1998; Latora and Marchiori, 2001). These concepts reconcile two long-standing opposing views of brain functioning. On the one hand are phrenology-based theories, which associated different cognitive tasks with segregated brain regions (Kanwisher, 2010). On the other hand are global workspace theories, which instead hypothesize the necessity of interareal integration of information to realize the same tasks (Dehaene and Naccache, 2001). Network science has provided the tools to quantify network segregation and integration by demonstrating, respectively, the presence of many clustered connections and few shortest paths between areas. More recently integration in the brain has been revisited and hypothesized to be determined by the presence of a few core hubs in the network, and not directly by the shortest paths (Deco *et al.*, 2015; Obando and De Vico Fallani, 2017). By considering multilayer brain networks, segregation and integration become a joint property of both nodes and layers, thus providing information about higher-order phenomena such as cross-frequency coupling (Jirsa and Müller, 2013), multimodal information (Garcés *et al.*, 2016), and temporal evolution (Hutchison *et al.*, 2013).

Tewarie *et al.* (2016) investigated information segregation and integration in MEG full multifrequency brain networks. They first observed the presence of strong dependencies between intralayer and interlayer connectivity. By decomposing the multilayers into representative connectivity structures, or "eigenmodes," they demonstrated that the overall amount of interlayer connectivity was associated with the second eigenmode, containing specific fronto-occipital network components common to all frequencies. In addition, they compared the empirical MEG multifrequency networks with those obtained from large-scale signals simulated with a thalamo-cortical model (Robinson *et al.*, 2001; Robinson, Rennie, and Rowe, 2002). By increasing the model structural coupling parameter, Tewarie *et al.* reported a progressive increase in the resulting functional interlayer connectivity. Real MEG multilayer networks maximally fit the model at the transition point of such an increment, suggesting an optimal balance between segregation and integration of information between different frequency bands.

As for multimodal connectivity, Battiston *et al.* (2018) investigated the associated integration properties by evaluating the core-periphery structure of DTI-fMRI multiplex networks. They specifically calculated the multiplex coreness (see Sec. III.B), which integrates information from different layers and provides a possibly more accurate characterization of the mesoscale brain network properties. Compared to the single-layer analysis, their results identified new core areas in the sensorimotor region of the brain that are key components of the so-called default mode network (DMN), i.e., a set of brain regions that is active when a person is not focused on the outside world (Raichle *et al.*, 2001). Besides, these results excluded previously established areas in the frontal region, whose inclusion in the core system was still being debated (Hagmann *et al.*, 2008). By including structural (DTI) and functional (fMRI) network information, these findings offered a new, enriched description of the integration properties of the human connectome's core (Fig. 7).

Temporal brain networks have been shown to exhibit alternating periods of segregation and integration across multiple timescales, associated with the presence of "dynamical" hubs (de Pasquale *et al.*, 2016), as well as state-dependent community structures (Al-Sharoa, Al-Khassaweneh, and Aviyente, 2019). To better understand the role of such transitions, Pedersen *et al.* (2018) studied the multilayer network flexibility (see Sec. III.B) derived from a large dataset of resting-state fMRI signals [Fig. 8(a)]. The results showed that the node flexibility, i.e., the frequency of community switching between consecutive time layers, was particularly high in specific associative brain regions (i.e., temporal and parietal) and correlated with the entropy of the connectivity variability. Because switching is known to increase in systems with high entropy or information load
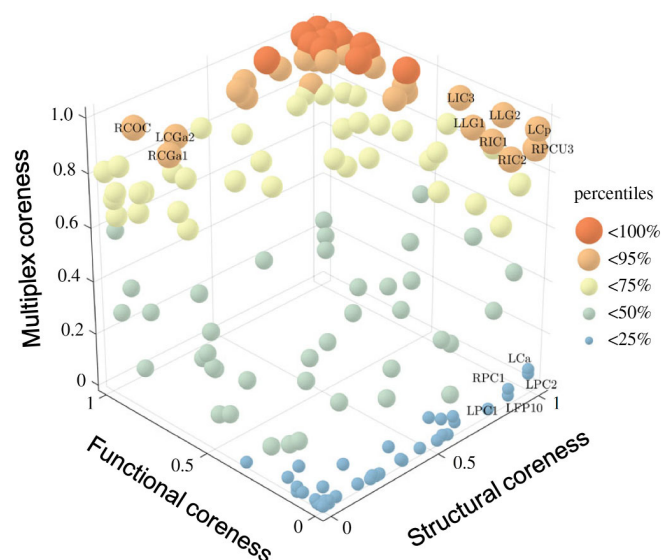

FIG. 7. Multiplex core-periphery structure of the human connectome. Scatterplot of multiplex coreness against single-layer corenesses obtained from structural (DTI) and functional (fMRI) layers. Labels indicate brain areas whose multiplex coreness cannot be predicted by looking at the coreness values in the respective structural and functional layers. Adapted from Battiston *et al.*, 2018.
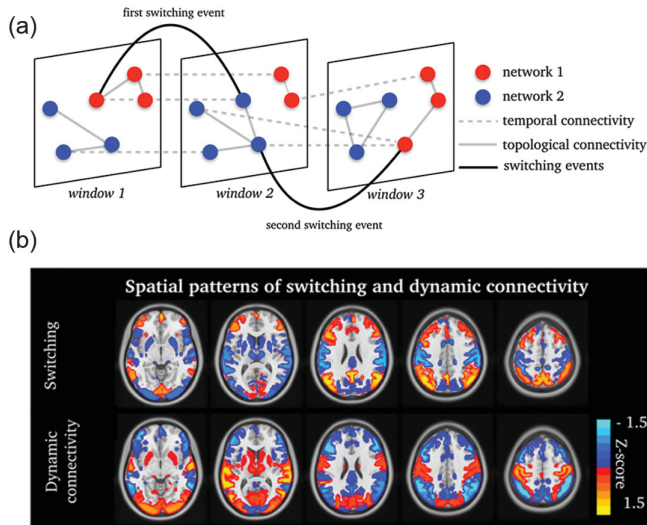
FIG. 8. Temporal network flexibility correlates with brain performance. (a) Overview of network switching (or flexibility) in a temporal network. The red and blue circles identify the nodes belonging to two different communities according to the multilayer network modularity metric. (b) Brain maps of switching rate and dynamic fMRI connectivity. Values were normalized into *z* scores to ensure that the connectivity dynamics and switching values were equally scaled. Adapted from Pedersen *et al.*, 2018.

(Amigó, Kloeden, and Giménez, 2013), the role of functional hubs for the associative cortex integrating information across differently specialized brain systems was eventually established (van den Heuvel and Sporns, 2011). These high local flexibility values occurred mainly when the brain exhibited a globally low and steady network intensity, so as to minimize the overall energetic cost associated with the integrative temporal switching [Fig. 8(b)].

On longer timescales, Malagurski *et al.* (2020) investigated how brain segregation changes with age using longitudinal fMRI data acquired over a four year time span. By computing the multiplex modularity [Eq. (7)], they showed that the global flexibility, i.e., the average node flexibility, is significantly higher in healthy elderly people than it is with a temporal null model, where the brain network layers are randomly shuffled (Chai *et al.*, 2016; Sizemore and Bassett, 2018). Their results also demonstrated that people with more segregated temporal networks tended to be more resistant to transient changes in modular allegiance (Meunier, Lambiotte, and Bullmore, 2010; Ramos-Nuñez *et al.*, 2017; Harlalka *et al.*, 2019). Advanced age was related to higher temporal variability in modular organization. However, no correlations were found with cognitive behavior, such as processing speed and memory encoding. Since flexibility is in general a good predictor of cognitive performance (see Sec. V.C), further studies should include more cognitive domains, or lagged changes, to elucidate the role of age in the relation between cognitive performance and temporal modular flexibility.

Taken together, these findings provide some concrete examples of how concepts such as segregation and integration of information can be broadened to capture multilayer brain mechanisms and provide complementary information about the system's behavior. While most studies have focused on

undirected connectivity, future research will be crucial to include directed links and obtain better information on communication pathways in neuronal systems (Avena-Koenigsberger, Misic, and Sporns, 2018).

C. Brain organizational properties of human behavior

The previously presented results aimed to quantify intrinsic structural and functional brain organization, with no reference to any specific mental state or behavior. Nonetheless, the brain is an extremely flexible and adaptive system capable of altering its organization depending on endogenous and exogenous stimuli coming from the external environment (a property often referred to as *plasticity*). Here we present some of the most recent results showing how multilayer brain network properties change according to specific behaviors, and how these higher-order topological changes are associated with intersubject variability.

Human learning is perhaps one of the most intriguing (and yet not completely understood) neural processes with numerous implications in our daily life (Zatorre, Fields, and Johansen-Berg, 2012; Barak and Tsodyks, 2014). A basic question in neuroscience is how learning is acquired through *Hebbian* plasticity without leading to runaway excitation of the neural synaptic activity (Miller and MacKay, 1994; Abbott and Nelson, 2000; Watt and Desai, 2010). Virkar *et al.* (2016) proposed a mechanism for preserving stability of learning neural systems via a two-layer network model. The first layer contained a model neural network interconnected by synapses that undergo spike-timing-dependent plasticity (STDP) (Feldman, 2012). The second layer contained a network model of glia cells interconnected via gap junctions, which diffusively transport metabolic resources to synapses (interlayer edges) [Fig. 9(a)]. The main results showed that, with appropriate model parameter values, the diffusive interaction between the two layers prevents runaway growth of synaptic strength, during both ongoing activity and learning. These findings suggest a previously unappreciated role for fast dynamic glial transport of metabolites in the feedback control stabilization of slow neural network dynamics during learning [Fig. 9(b)]. Notice that this is one of the few examples to date in which multilayer network theory is used to model microscale neural organization across multiple temporal scales.

At larger spatial scales, Bassett *et al.* (2011) used a multilayer network approach to characterize human learning during a simple motor task. In particular, they built temporal brain networks from fMRI signals across consecutive experimental sessions. They used multiplex modularity [Eq. (7)] to find long-lasting modules and found that community organization changed smoothly with time, displaying coherent temporal dependence, as in complex long-memory dynamical systems (Achard *et al.*, 2008). Their results also showed that network flexibility changed during learning (first increasing and then decreasing), thereby demonstrating a meaningful biological process. In particular, the nodal flexibility (see Sec. III.B) was stronger in frontal, posterior parietal, and occipital regions. In addition, their results predicted the relative amount of learning from one session to the next (Fig. 10). These predictions could not be obtained via conventional task-related fMRI activation or standard network
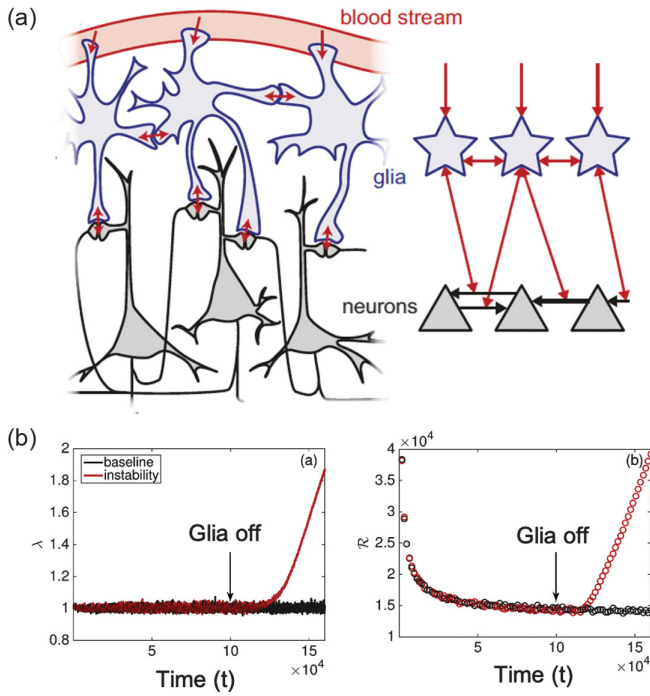
(a)

(b)

FIG. 9. Stabilization of critical dynamics in multilayer glia-neuronal networks. (a) Left side: glia cells redistribute metabolic resources from the bloodstream to neural synapses. Right side: associated two-layer network model. Black arrows indicate neural synaptic interactions. The arrow thickness indicates the synaptic strength that evolves according to spiking-time-dependent plasticity (STDP). Red arrows that terminate on black arrows represent the resource supply to the corresponding synapse. (b) Stability analysis of the two-layer STDP model. The largest eigenvalue λ of the neuronal network layer and the total resource $\mathcal{R}$ of all glia and synapses are illustrated as a function of time. The data plotted in black correspond to a "baseline" condition. For the data plotted in red (labeled "instability"), the initial evolution is the same as that for the baseline data until the diffusion of resources between the glial cells is turned off (vertical arrow). Adapted from Virkar *et al.*, 2016.
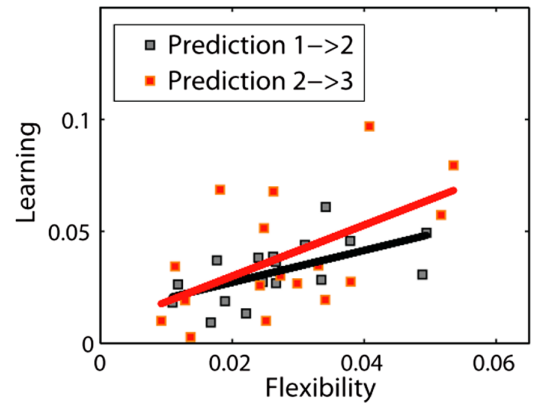

FIG. 10. Temporal network flexibility predicts future learning rate. Significant predictive Spearman correlations between flexibility in session 1 and learning in session 2 (black curve, $p \approx 0.001$) and between flexibility in session 2 and learning in session 3 [red (lighter gray) curve, $p \approx 0.009$]. Each point corresponds to a subject. Note that the relationships between learning and fMRI network flexibility in the same experimental sessions (1 and 2) were not significant; $p > 0.13$ was obtained using permutation tests. Adapted from Bassett *et al.*, 2011.

analysis, and they confirmed the relation between network flexibility and cognitive performance. Indeed, network flexibility has been found to correlate not only with several mental states, such as working memory and planning (Braun *et al.*, 2015; Pedersen *et al.*, 2018), but also with mental fatigue (Betzel *et al.*, 2017) and sleep deprivation (Pedersen *et al.*, 2018). At this stage, it would be interesting to elucidate whether network flexibility is an aspecific predictor of cognitive performance or whether it can also distinguish between different dynamic brain states.

Makarov *et al.* (2018) further studied the cognitive load during attentional tasks in an EEG frequency-based multiplex framework. Based on betweenness centrality (see Sec. III.B), they observed an outflow of the shortest paths from low frequencies to high frequencies in the frontoparietal regions. These findings suggest that cross-frequency integration of information not only is an intrinsic characteristic of brain functioning (Tewarie *et al.*, 2016) but is also modulated by attentional tasks as well as drowsiness (Harvy *et al.*, 2019).

In a recent study, Williamson, Domenico, and Kadis (2021) investigated how the brain supports expressive language

function by looking at MEG multifrequency brain networks. In particular, they aimed to identify the brain regions that are important for successful execution of expressive language in typically developing adolescents. To this end, they first identified the multifrequency hubs by means of a modified version of the multilayer PageRank centrality and then reranked them according to their importance in fostering interlayer communication. Compared to a standard single-layer analysis, this two-step procedure allowed them to capture nonlinear interactions and resolve the task-related brain areas with a higher spatial resolution. These regions lay mostly in the left hemisphere and represented possible conduits for interfrequency communication between action and perception systems that are crucial for language expression (Pulvermüller, 2018).

Planning and executing motor acts is accompanied by changes in brain activity and connectivity on short timescales of the order of milliseconds (Pfurtscheller and Lopes da Silva, 1999; Svoboda and Li, 2018). Tang *et al.* (2010) used an EEG temporal network approach to characterize such fast brain functional organization during a simple foot movement task. Compared to network sequences with randomly shuffled layers, brain networks showed a higher temporal clustering and a similar characteristic temporal path length; see Sec. III.B. Put differently, dynamic brain networks exhibited a temporal small-world propensity, supporting both segregation and integration of information through time. While a single-layer analysis previously unveiled that segregation and integration properties fluctuate and adapt over the different phases of the movement (De Vico Fallani *et al.*, 2008), these findings provided new evidence of the intrinsic global temporal properties of motor-related brain networks.

VI. MULTILAYER NETWORK-BASED BIOMARKERS OF BRAIN DISEASES

Like any other complex system, the brain can exhibit anomalous connectivity, which in turn may lead to abnormal

behavior and clinical symptoms. These brain connectivity changes can be spatially distributed, as in schizophrenia or Alzheimer's disease, or localized, as in stroke or traumatic injuries (Hallett *et al.*, 2020). Looking at the network organization under both healthy and diseased conditions therefore appears to be fundamental to understanding the resilience and vulnerabilities of the brain (Russo *et al.*, 2012). From a medicine perspective, network-based biomarkers would represent advanced tools to monitor the disease progression and inform new therapeutics to mitigate or counteract the effects of the disease. In the last decade, standard network analysis has accumulated evidence documenting general reorganizational properties such as a departure from optimal small-world configurations, aberrant modular reorganization, and a significant loss of node centrality (Stam, 2014). Thus far these network changes have remained associated with a particular aspect, or layer, of information. Since brain pathologies typically result from multifactor processes at different scales and levels, multilayer brain networks naturally constitute a more appropriate integrative modeling approach. In the following, we present some of the most recent results obtained for different brain diseases. They provide new perspectives on the impacted multiscale network properties and can be used to improve diagnoses and predictions.

A. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common form of dementia. Clinically, it is characterized by mild memory impairments that gradually evolve up to severe cognitive impairments, and eventually to death. In 2016, people affected by AD and other dementias numbered around 44 million worldwide, and this incidence is likely to increase because of longer life expectancies (Nichols *et al.*, 2019). At the cellular level, AD is characterized by the progressive accumulation of τ tangles and β-amyloid plaques that cause neurons and synapses to die, thus leading to brain atrophy and disordered disconnection patterns.

While the consequences of these changes on large-scale brain networks have been widely investigated, the accumulated results are often discordant and depend on the considered spatial or temporal scale (Tijms *et al.*, 2013; Gaubert *et al.*, 2019). Multilayer networks represent an interesting approach to get an integrated, potentially more informative picture of the disease.

Multiplex networks have been used to provide a unified description of AD brain reorganization across multiple MEG frequency bands [Fig. 11(a)]. Yu *et al.* (2017a) used different multiplex nodal metrics (such as overlapping clustering, local efficiency, and betweenness centrality; see Sec. III.B) and consistently showed that physiological multilayer hub regions, including posterior parts of the DMN, were severely impacted by AD [Fig. 11(b)]. Note that these losses of functional hubs could not be observed when individual frequency layers were considered. These multilayer hub disruptions correlated not only with the accumulation of β-amyloid plaques in the cerebrospinal fluid but also with the cognitive impairment of the patients, thus demonstrating a potential clinical relevance. When the multiplex participation

coefficient [Eq. (3)] was used, the results indicated that the most vulnerable hub regions in patients with AD also lost their ability to foster communication across frequencies compared to those regions in healthy control subjects. Similar results obtained independently by Guillon *et al.* (2017) showed a significant loss of multifrequency hubs in DMN regions and a strong association with memory impairment. Using a classification analysis, they eventually showed that integrating multiparticipation coefficient values with equivalent single-layer network metrics leads to improved distinguishability of AD and healthy subjects. More recently Echegoyen *et al.* (2021) showed that AD patients could be identified by the lower values of algebraic connectivity λ_2 (see Sec. IV.B) in resting-state MEG multifrequency networks. These results single out new network mechanisms that hinder information load from flowing through different frequency bands and eventually impair the cognitive abilities of AD patients.

Cai *et al.* (2020) addressed similar questions in EEG multifrequency brain networks. They showed that both multiplex clustering [Eq. (4)] and multiparticipation coefficients [Eq. (3)] presented significant decrements with respect to healthy controls in the posterior areas of the brain. These results confirmed a general tendency in AD patients to loose segregation and integration of information capabilities across signal frequencies. Yet few observed increases in frontal areas suggest the presence of some compensatory mechanisms to be further elucidated (Guillon *et al.*, 2019). In the same study, Guillon *et al.* also investigated the dynamic aspects of EEG brain networks in AD from a purely temporal perspective [Fig. 11(a)]. Using the aforementioned multilayer metrics, they showed that AD temporal segregation was impacted mostly by AD in the frontal and occipital areas, while temporal integration properties were less affected than they were in healthy subjects, mainly because of its higher variability across nodes. However, when combined together, nodal values of temporal segregation and integration led to a high discrimination between AD and healthy subjects ($> 90\%$ accuracy), suggesting that spatial heterogeneity of temporal integration may also be related to progression of the disease [Fig. 11(c)].

To integrate and disentangle the role of different neuroimaging modalities in AD, Guillon *et al.* (2019) built multiplex networks composed of different connectivity types derived from diffusion-weighted imaging (DWI), fMRI, and MEG data. Thus far this represents the most complete type of multiplex brain network merging together structural and functional information [Fig. 12(a)]. By focusing on the mesoscale properties (see Sec. III.B), Guillon *et al.* showed a selective reduction of multiplex coreness in the AD population involving mainly temporal and parietal hub nodes of the DMN that are typically impacted by the anatomical atrophy and β-amyloid plaque deposition (Chételat *et al.*, 2010). This significant loss was driven mainly by a few layers, notably DWI, fMRI, and MEG in the alpha 1 (7–10 Hz) frequency range, and could be explained by a simple model reproducing the progressive random disconnection of the multilayer network via the preferential attacks of its core hubs [Fig. 12(b)]. From a clinical perspective, Yu *et al.* (2017a) eventually reported that patients with larger coreness disruptions tended to have more severe memory and cognitive impairments, which is in line with the general tendency
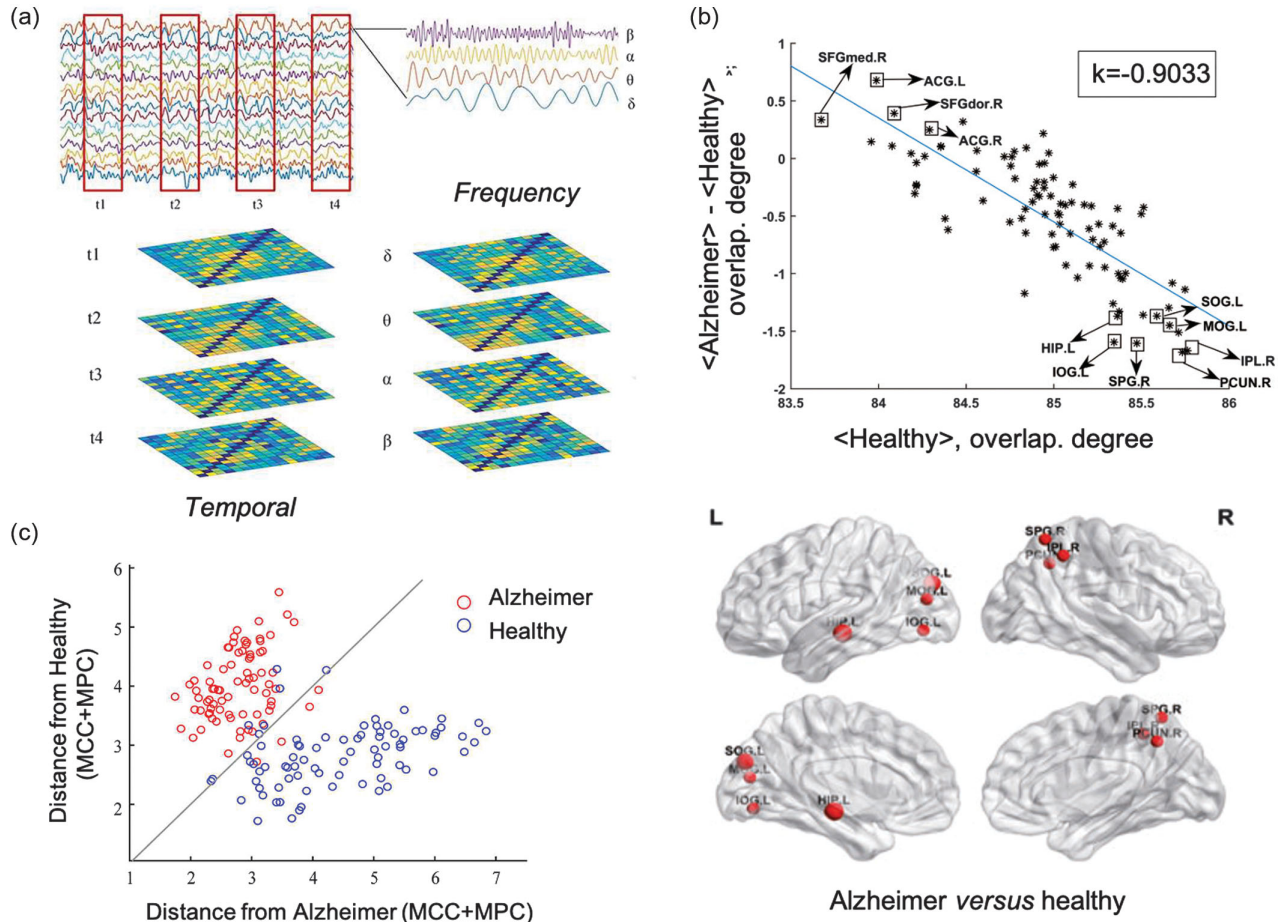
FIG. 11.   Multifrequency and temporal reorganization of brain networks in Alzheimer's disease. (a) Multiplex brain networks are constructed by layering different frequency-specific networks, while temporal networks were constructed by concatenating time-specific networks within frequency bands. (b) Top: hub disruption of MEG multifrequency networks in patients with Alzheimer's disease. Each point corresponds to a different brain area, and *k* is the slope of the regressing line. Bottom: brain regions with significant between-group differences in the overlapping weighted degree. PCUN.R, right precuneus; HIP.L, left hippocampus; IPL.R, right inferior parietal but supramarginal and angular gyri; SPG.R, right superior parietal gyrus; MOG.L, left middle occipital gyrus; SOG.L, left superior occipital gyrus; IOG.L, left inferior occipital gyrus. Adapted from Yu *et al.*, 2017a, and Cai *et al.*, 2020(c) Scatterplot showing the Mahalanobis distance of each subject from the AD or control group when the multiplex clustering coefficient (MCC) and the multiplex participation coefficient (MPC) extracted from time-varying networks (gray line indicates equal distance) are combined. Adapted from Cai *et al.*, 2020.

observed in other previously described studies [Fig. 12(c)]. Recently Canal-Garcia *et al.* (2022) built two-layer multimodal networks from gray matter atrophy and amyloid deposition across different stages of AD in humans. In a rigorous, controlled study, they provided specific results that are not obtainable with traditional approaches from single imaging modalities. Multiplex modularity [Eq. (7)] revealed a characteristic module in the temporal brain area that likely reflects the transition to AD dementia. Decreased values of multiplex participation coefficients [Eq. (3)] in atrophy-related hub regions were also found in the later AD stage compared to those found in healthy control subjects. This study sheds light on the nontrivial interplay between β-amyloid level and gray matter atrophy and its clinical relevance for AD.

Taken together these results indicate that AD is characterized by a previously unappreciated multimodal and temporal disconnection mechanism that primarily affects regions impacted by the atrophy process. Future research will be crucial to elucidate whether such a disruption tendency is compensated for by other multilayer mechanisms, possibly involving more intact cortical systems such as the sensorimotor one (Albers *et al.*, 2015; Kubicki *et al.*, 2016; Guillon *et al.*, 2019).

B. Neuropsychiatric disorders

Among neuropsychiatric disorders, schizophrenia is certainly one of the most studied due to its large population incidence. In 2017, more that 20 million people were suffering from schizophrenia worldwide (James *et al.*, 2018). Typical clinical symptoms include hallucinations, emotional blunting, and disorganized speech and thoughts. The biological causes of schizophrenia are still poorly understood, and many hypotheses are currently being investigated based on neurotransmitter dysregulation (Lang *et al.*, 2007), myelin reduction
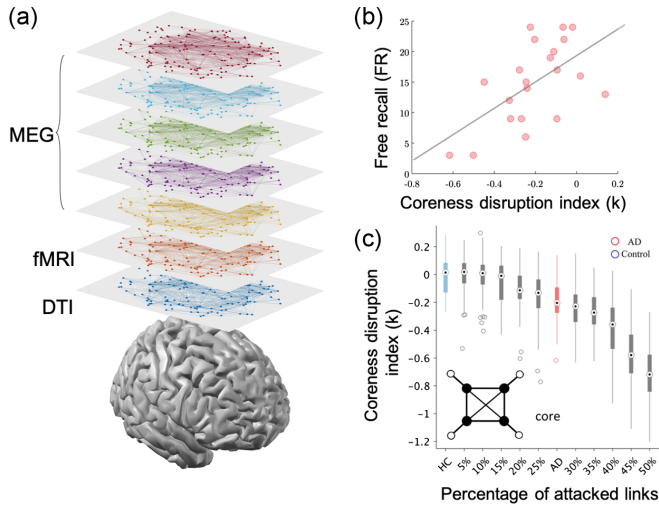
FIG. 12.   Multimodal brain networks revealing disrupted core-periphery structure in Alzheimer's disease. (a) Multimodal brain networks (multiplex) constructed by layering DTI, fMRI, and several frequency-based MEG brain connectivities. Adapted from Guillon *et al.*, 2017. (b) Spearman correlation ($R = 0.59$, $p = 0.005$) between the coreness disruption index (κ) and the memory impairment of AD patients as measured using the free recall (FR) test. (c) Box plots showing the values of the coreness disruption index (κ) obtained by progressively removing the edges preferentially connected to the multiplex periphery of the healthy control (HC) group. The blue (*x*-axis HC) and red (*x*-axis AD) box plots illustrate, respectively, the κ values for the HC and AD groups. (b),(c) Adapted from Guillon *et al.*, 2019.

(Cassoli *et al.*, 2015), and oxidative stress (Steullet *et al.*, 2016). At large spatial scales, low and high frequency neuronal oscillations, as well as their interactions, have been widely documented as a core feature of the neuropathology underlying schizophrenia (Moran and Elliot Hong, 2011). Functional connectivity changes within and between frequency bands have been reported in schizophrenic patients (Siebenhühner *et al.*, 2013) and have been associated with persistent symptoms leading to disorganization of visuomotor mental functions (Brookes *et al.*, 2016).

Using a multiplex approach, De Domenico, Sasai, and Arenas (2016) provided the first integrated characterization of the topological changes in schizophrenia from resting-state fMRI-derived multifrequency networks. In particular, they evaluated the multiplex PageRank centrality (see Sec. III.B) and showed a substantial reorganization of the most important multifrequency hubs of the brain, including the precuneus cortex, a key region for the basic physiological brain organization (van den Heuvel and Sporns, 2013). When injected into a random forest classifier, multiplex PageRank centrality metrics led to a classification accuracy of 80%, which is higher than standard network approaches but comparable to otherwise much more sophisticated machine learning techniques. At cellular levels, schizophrenia has been hypothesized to result from excitatory-inhibitory neuronal dysfunction, with a consequent abnormal temporal coordination between large-scale macroscale areas of the cerebral cortex (Uhlhaas and Singer, 2010; Uhlhaas, 2013). When investigating temporal fMRI networks, Braun *et al.* (2016) showed that schizophrenic
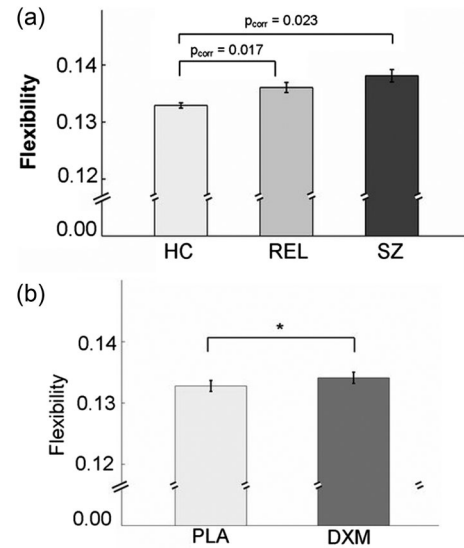

FIG. 13.   Temporal network flexibility as a clinical marker of schizophrenia genetic risk. (a) Significant increases in the mean dynamic reconfiguration of modular fMRI brain networks in unaffected first-grade relatives (REL) (gray bar) and patients with schizophrenia (SZ) (black bar) compared to matched healthy controls (HC) (white bar) [$F(2, 196) = 6.541$, $P = 0.002$]. Bars indicate mean values, and whiskers represent standard error means (SEMs). (b) Significant increases in the mean dynamic reconfiguration of modular brain networks in healthy controls after application of dextrometorphan (DXM) [dark gray bars; repeated measures ANOVA placebo (PLA) vs DXM: $F(1, 34) = 5.291$, $P = 0.028$] relative to PLA (light gray bars). Adapted from Braun *et al.*, 2016.

patients exhibited a multiplex network flexibility increase (see Sec. III.B) compared to healthy subjects during a working memory task, which is typically used to assess the neural basis of cognitive deficits (Meyer-Lindenberg *et al.*, 2001, 2005) [Fig. 13(a)]. Braun *et al.* were able to reproduce the same *hyperflexibility* while experimentally blocking the glutamate sensible synaptic receptors (NMDA receptors) in a separate group of healthy subjects [Fig. 13(b)]. These results were further confirmed in a subsequent work, which localized such network hyperflexibility in specific brain zones including cerebellum, thalamus, and frontoparietal task-related areas (Gifford *et al.*, 2020). Altogether these findings indicated for the first time that microscale excitatory-inhibitory imbalances in schizophrenia might actually translate into temporally less stable and possibly disintegrated (rather than overly rigid) large-scale brain reorganization.

From a pure classification perspective, multilayer brain networks have also been used as alternative multidimensional features to better discriminate between schizophrenic and healthy subjects. Lombardi *et al.* (2019) considered a working memory fMRI experiment and built a 17-layer multiplex brain network where each layer contained a different type of nonlinear functional connectivity. For each layer they extracted standard nodal centrality metrics (i.e., strength, betweenness, clustering, and PageRank) and used them as classification features. Compared to single-layer networks built from simple linear correlations, they achieved a significantly higher classification ($\approx$90% vs $\approx$70%) for different

types of working memory tasks. Pursuing the same goal, Wilson *et al.* (2021) considered resting-state fMRI data on a group of healthy individuals and a group of patients with schizophrenia. Originally, they built a multiplex brain network for the two groups, where each layer represented the functional network of a specific individual. By extending the well-known `node2vec` unsupervised network embedding procedure (Grover and Leskovec, 2016), they learned continuous node feature representations from multilayer networks based on random walkers that are allowed to move across layers. The resulting embeddings revealed a higher variability for the similarity between the nodes in the default mode network and salience subnetwork, suggesting a less stable within-module brain organization in the schizophrenic group. While the overall classification accuracy did not outperform state-of-the-art performance, learning the features in an unsupervised approach may nevertheless be important for future applications in automatic diagnosis.

Major depressive disorder (MDD) is clinically characterized by severe fatigue, aphasia, difficulty focusing, and suicidal thoughts in extreme cases. Symptoms are diverse and their severity largely differs among patients. Since effective treatments are currently available, scientific research focuses mostly on identifying predictive biomarkers to enable more personalized therapeutics. Previous studies suggested that MDD leads to several brain signal alterations affecting functional connectivity within but also between different frequency bands (Tian *et al.*, 2019; Nugent *et al.*, 2020). To fully exploit this multifrequency information, Dang *et al.* (2020) proposed a full multilayer approach to improve the diagnosis of MDD. Specifically, they developed a convolutional neural network that directly takes as input the full multilayer brain networks to learn and extract the most discriminant features. The resulting classification accuracy ($\approx$97%) was comparable to state-of-the-art methods based on specific frequency bands. While promising, these findings suggest that machine learning algorithms for multilayer brain networks still have to be fine-tuned in view of their concrete implication in the identification of the best intervention strategy to cure or alleviate MDD-related symptoms.

C. Other neurological diseases

Epilepsy is a group of neurological disorders characterized by seizures, which may vary in time and intensity from short, mild loss of awareness to long, vigorous convulsions. Epileptic seizures are characterized by excessive synchronized neuronal activity in the entire cerebral cortex or in parts of it. In 2017, about 27 million people were suffering from epilepsy (James *et al.*, 2018), of whom 30% were not curable with drug treatment (Kwan and Brodie, 2000). Clinical research aims mostly at identifying predictive neural markers of the seizures to allow preventive treatments or to localize the origin of the seizure to inform precise surgery (Engel *et al.*, 2013).

Recent evidence has shown that epilepsy seizures are characterized by brain functional connectivity changes within, but also between, different brain signal frequencies (Villa and Tetko, 2010; Jacobs *et al.*, 2018; Samiee *et al.*, 2018). From a topological perspective, decrements of network efficiency have been reported between low and high frequency bands,

before the seizure onset, and were associated with sensorial disturbance and mild loss of consciousness (Yu *et al.*, 2020).

The intrinsic relationship between structural and functional layers can also unveil hidden connectivity structures characterizing different types of epilepsy. Along these lines, Huang *et al.* (2020) used a DTI-fMRI multiplex approach to classify between epileptic seizures originating in different zones of the brain, namely, the frontal and temporal lobes. In particular, they extended the concept of multiplex motifs to include subgraphs with more than three nodes; see Sec. III.B. The most frequent multiplex patterns consisted of edges from both structural and functional layers that were spatially localized. The structural components were stable across conditions and involved regions belonging to the DMN system (i.e., cuneus, precuneus, and peripheral cortex) (Horn *et al.*, 2014). Instead, the functional counterparts of the multiplex patterns were highly variable and predominantly involved regions concentrated in the respective epileptogenic zones, i.e., the temporal and frontal lobes. Eventually, Huang *et al.* demonstrated the superiority of these multiplex connectivity patterns to discriminate between epileptic patients and healthy controls (72%–82% classification accuracy) over equivalent single-layer metrics or other multiplex metrics such as multiplex PageRank or algebraic connectivity; see Sec. III.B. These results are in line with the one-to-many relationships between structural and functional brain networks (Park and Friston, 2013) and can be used to fine-tune the research of predictive biomarkers in epilepsy.

Consciousness disorders regroup a variety of symptoms that range from a complete loss of awareness and wakefulness, such as coma, to minimal or inconsistent awareness (Giacino *et al.*, 2014). The differential diagnosis between the different types of disorders of consciousness is paramount for identifying the best medical therapeutics. Recent results suggest that frequency-dependent functional brain connectivity is crucial for characterizing impairments of consciousness, as well as predicting possible recovery processes (Chennu *et al.*, 2014; Corazzol *et al.*, 2017; Cacciola *et al.*, 2019). In an effort to provide a unified picture on the role of brain connectivity within and between frequency bands, Naro *et al.* (2021) adopted a multilayer network approach. By investigating brain networks derived from source-reconstructed EEG signals, they aimed to distinguish between patients suffering from unresponsive wakefulness syndrome (UWS) and those afflicted with a minimally conscious state (MCS), two conditions that often present similar symptoms (Stender *et al.*, 2014). Results showed that several nodal multiplex metrics, including overlapping clustering, betweenness, and multiplex participation coefficient (see Sec. III.B), were significantly lower in UWS than in MCS patients. This was particularly evident in the frontoparietal regions of the brain whose relative loss of multiplex centrality is associated with the behavioral responsiveness of the patients quantified by the coma recovery scale (Giacino, Kalmar, and Whyte, 2004). By adopting a full multilayer network approach, Naro *et al.* (2021) eventually reported a significantly lower interlayer connection intensity in the UWS group and could identify those patients who regained consciousness one year after the experiment. The discrimination between UWS and MCS patients was not observed when looking separately at frequency-specific

network layers. Although preliminary, these results demonstrated the clinical value of considering multiplex or multilayer network approaches to derive more reliable neuro-markers of consciousness disorders.

VII. EMERGING PERSPECTIVES

We have presented novel conceptual insights, tools, and results that provide new perspectives on the intrascale and interscale network properties of brain systems. Research in the field is active, and many issues remain to be addressed in the future for ultimately characterizing the multiscale, multi-level brain organization. We close this Colloquium by focusing on three broad directions of advances in multilayer network theory that we find particularly relevant for addressing this gap.

A. Generative models of multiscale networks

Generative models for brain networks allow one to move from descriptive top-down approaches to mechanistic bottom-up ones (Betzel and Bassett, 2017a). These models usually define a set of local connection rules (such as probabilistic rewiring or preferential attachment) to grow synthetic networks with specific global properties (such as small worldness or scale-free degree distribution). Network models in neuroscience have been driven mostly by biological and topological evidence or hypotheses (Vértes *et al.*, 2012; Betzel *et al.*, 2016).

Biologically inspired models have primarily implemented minimal wiring cost principles (Bullmore and Sporns, 2012) and have been used to reproduce the rich-club organization of brain networks (Vértes, Alexander-Bloch, and Bullmore, 2014), to characterize the phase transition of axonal growth (Nicosia *et al.*, 2013), and to determine genetic risk factors associated with schizophrenia (Zhang *et al.*, 2021). Topologically inspired models focused instead on reproducing the organizational properties of brain networks and have been adopted to identify the local connection mechanisms of network integration and segregation (Simpson, Moussa, and Laurienti, 2012; Sinke *et al.*, 2016; Obando and De Vico Fallani, 2017) or to reproduce the mesoscale modular properties of brain networks (Betzel, Medaglia, and Bassett, 2018).

The development of multilayer network models therefore appears to be a crucial step toward the multiscale modeling of the brain from a network perspective. On the one hand, experimental technology is increasingly providing new data on different levels of neuronal interactions through 3D neuronal cultures (Hopkins *et al.*, 2015), calcium dynamics (Ahrens *et al.*, 2013), spiking activity (Jun *et al.*, 2017), and vascular support (Mac *et al.*, 2011; Kirst *et al.*, 2020) and might offer precious spatiotemporal insights to test biologically plausible multilayer connection criteria. On the other hand, we are currently witnessing a research thrust in the mathematical formalization of generative multilayer network models, inspired mostly by topological criteria.

For example, Bazzi *et al.* (2020) recently proposed a unifying probabilistic framework to generate multiplex networks with any type of modular structure that explicitly incorporates a user-specified tunable dependency between network layers. These models might be useful to better quantify and understand the generation of mesoscale properties in multi-modal and temporal brain networks. Based on the extension of stochastic block models (Peixoto, 2014), where nodes connect to each other with probabilities that depend on their group memberships, Vallès-Català *et al.* (2016) proposed an original approach to derive the most likely multiplex modular network associated with any observed single-layer network. Alternatively, Lacasa *et al.* (2018) provided a robust method relying on the Markovian diffusion of a random walker to determine whether a complex system is better modeled by a single interaction layer or by the interplay of multiple layers. All these frameworks look particularly appealing for multi-scale modeling, as they might be used to identify the mesoscale inner workings of connectivity aggregation across different layers. Finally, multilevel exponential random graph models potentially represent the most powerful framework due to their ability to characterize arbitrary connection patterns forming within and between layers, and to reproduce full multilayer networks (Wang *et al.*, 2013). This decade will be crucial for elucidating how multilevel biological knowledge and multilayer network tools can be merged to establish a new generation of network-based multiscale models of brain organization.

B. Controllability of multilayer networks

Understanding a complex system means being able to describe it, reproduce it, and ultimately control it (Liu and Barabási, 2016). In the last decade, the development of network control theory applied to brain connectivity has led to a paradigm shift, offering new tools to understand how the brain controls itself and how it can be controlled by exogenous events (Tang and Bassett, 2018).

Although still debated as to the way it should be implemented and interpreted (Tu *et al.*, 2018; Jiang and Lai, 2019), network controllability has allowed researchers to identify the *driver* nodes that are more likely to steer the activity of human brain networks, opening up substantial possibilities for cognitive and clinical neuroscience, such as via brain stimulation technology (Khambhati *et al.*, 2016; Muldoon *et al.*, 2016; Tang and Bassett, 2018). More recently a network control framework was also used to determine the role of each *C. elegans* neuron in locomotor behavior, which was confirmed by *a posteriori* laser ablations (Yan *et al.*, 2017). While the development of network controllability for single-layer systems is in its adolescence, its extension to multilevel systems is still in its infancy.

The application to temporal networks is perhaps the most intuitive extension of structural controllability. By considering the discrete time-varying linear dynamics of the system, Pósfai and Hövel (2014) provided computational tools to study controllability based on temporal network characteristics. They specifically investigated the ability of single driver nodes to control a target and showed that the overall activity and the node degree distribution of the temporal network are the main features influencing controllability. Although it might seem that static links would make it easier to control a system, Li *et al.* (2017) demonstrated that temporal networks can be controlled more efficiently and require less energy than

their static single-layer counterparts. Using higher-order network models, Zhang, Garas, and Scholtes (2021) also showed that the chronological ordering of interactions has a strong influence on the time needed to fully control the network.

Determining the energy needed by the driver nodes to steer the system is also crucial. Excessively energetic control signals could be impossible to produce or could merely damage the system itself. In the case of full multilayer networks, Wang and Zou (2017) demonstrated that there is a trade-off between the optimal controllability and optimal control energy that depends on the configuration and intensity of the interlayer connection patterns. In a separate study, Menichetti, Dall'Asta, and Bianconi (2016) showed that controlling multiplex networks is more costly than controlling single layers taken in isolation, and that multiplex networks can exhibit stable controllability regardless of the stability of their layers. They also reported that in general multiplex networks need more drivers and that this number depends on the degree correlations between low-degree nodes in the different layers. Collectively, these findings encourage the development of controllability tools for multilayer brain networks, with the goals of better disentangling the interaction between multiple scales and improving the efficacy of possible intervention strategies.

C. Machine learning and multilayer networks

Network science is a successful approach to analyzing and modeling complex systems and uncovering mechanisms that explain the emergence of functions. However, network theory alone often fails to efficiently manipulate large datasets as well as different levels of resolution. It is important to note that it focuses on specific *handcrafted* topological features and ignores less intuitive but possibly existing representative patterns, such as higher-order network interactions (Battiston *et al.*, 2020).

In this regard, machine learning represents a powerful technique for handling large amounts of data and learning from the data itself the hidden patterns associated with the intrinsic phenomena of the system (Bishop, 2006). As a counterpart, machine learning ignores the fundamental laws of physics and can result in ill-posed problems or noninterpretable solutions. The combination of machine learning and network science therefore represents a potential win-win strategy to address the previously mentioned limitations, as demonstrated in a number of theoretical works and applications (Zanin *et al.*, 2016; Muscoloni *et al.*, 2017). Nonetheless, when it comes to multiscale modeling, the type of algorithms must be rethought and extended to take into account the multilayer nature of the system, properly integrate the within- and between-layer concepts, and explore the extremely large feature spaces (De Domenico, Lancichinetti *et al.*, 2015; Alber *et al.*, 2019).

Based on a specific class of deep learning algorithms, Dang *et al.* (2020) developed a convolutional neural network that directly takes as input a full EEG multifrequency network to learn and extract the most discriminant features. The core of their algorithm consisted of three consecutive convolutional layers, one batch normalization layer and one pooling layer. This combination of basic hidden layers could effectively avoid overfitting and speed up the model training. Eventually, all learned features were concatenated together for classification between healthy and major depressive diseased subjects.

Machine learning can be optimized to operate feature engineering and embed the original multilayer network into a low-dimensional space so as to allow a minimal representation of the main intrinsic properties of the system. Based on the `node2vec` algorithm (Grover and Leskovec, 2016), Wilson *et al.* (2021) introduced a fast and scalable extension, called `multi-node2vec`, that learns the nodal features from complex multilayer networks through the skip-gram neural network model (Fig. 14). This model was originally designed to extract the features of a word's neighborhood in text and was then adapted to characterize the neighborhood of nodes in a network (Mikolov *et al.*, 2013). Applying the
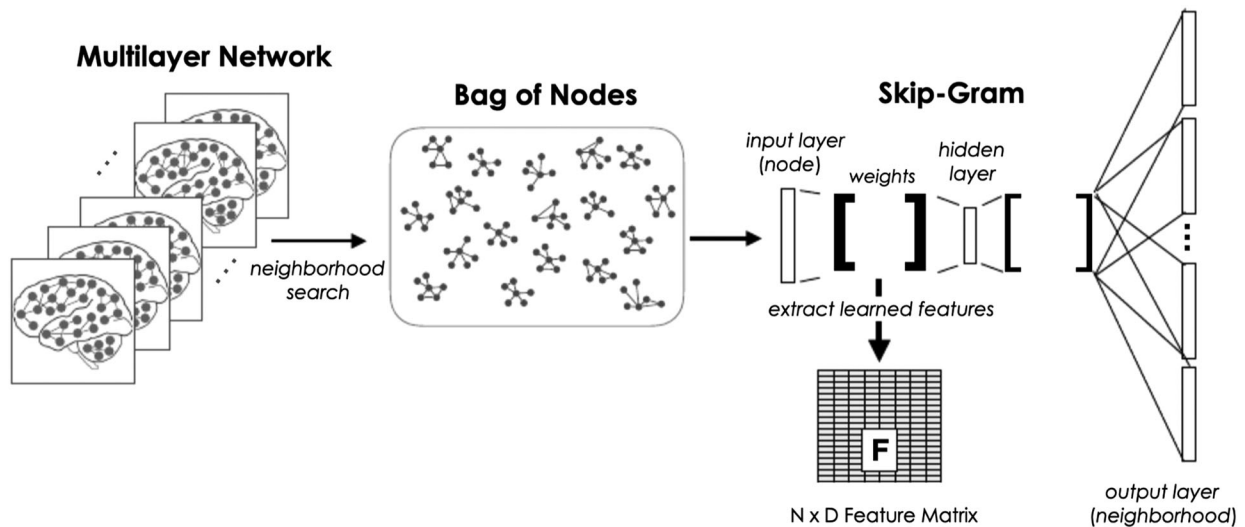

FIG. 14. Illustration of the `multi-node2vec` algorithm. Beginning with a multilayer network (left), one first identifies a collection of multilayer neighborhoods (bag of nodes) via the variable neighborhood search procedure. Next, the optimization procedure calculates the maximum likelihood estimator F through the use of the skip-gram neural network model (right) on the identified bag of nodes. Adapted from Wilson *et al.*, 2021.

model to fMRI multisubject networks, Wilson *et al.* showed that it improves the visualization and clustering of brain regions into communities of similar features and discriminates between schizophrenic and healthy groups of subjects.

More generally, the community detection task of partitioning the nodes of a multilayer network into densely connected subgroups, or communities, can also be viewed as a particular multilayer embedding. The development of multilayer community detection methods is still in its early stages, but several useful techniques have been developed in the past decade (Mucha *et al.*, 2010; De Domenico, Lancichinetti *et al.*, 2015; Stanley *et al.*, 2016; Wilson *et al.*, 2017).

VIII. CONCLUSION

Understanding brain organization ultimately requires one to quantify the interactions within and between multiple levels of neural structure and dynamics. In the last decade, multilayer network theory has been introduced to characterize complex systems exhibiting different levels, or layers, of connectivity as well as cross-level interactions. Here we have presented and discussed many new developments in the field of multilayer network theory for the study of multiscale brain organization. We anticipate that, in conjunction with more accurate experimental technologies and increasing computational power, multilayer network theory can eventually become a key component of modern multiscale brain modeling. Through this Colloquium, we hope to have provided fresh elements to stimulate new ideas in scientists and practitioners wanting to advance multiscale brain modeling, which has profound implications for the betterment of our health and cognitive function.

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