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REVIEW ARTICLE

Cognitive function: holarchy or holacracy?

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Abstract

Cognition is the most complex function of the brain. When exploring the inner workings of cognitive processes, it is crucial to understand the complexity of the brain's dynamics. This paper aims to describe the integrated framework of the cognitive function, seen as the result of organization and interactions between several systems and subsystems. We briefly describe several organizational concepts, spanning from the reductionist hierarchical approach, up to the more dynamic theory of open complex systems. The homeostatic regulation of the mechanisms responsible for cognitive processes is showcased as a dynamic interplay between several anticorrelated mechanisms, which can be found at every level of the brain's organization, from molecular and cellular level to large-scale networks (e.g., excitation-inhibition, long-term plasticity-long-term depression, synchronization-desynchronization, segregation-integration, order-chaos). We support the hypothesis that cognitive function is the consequence of multiple network interactions, integrating intricate relationships between several systems, in addition to neural circuits.

Keywords Cognitive function · Networks · Open complex systems · Anticorrelated mechanisms

Introduction

From the concept of "*diaschisis*" introduced by von Monakov in 1914 to the novel idea of alterations of brain connectomics [1], cognitive dysfunction can be described as an imbalance of all three levels of brain's structural and functional organization: molecular/cellular level, local circuits' level, and large-scale network level. Each one of these levels interacts dynamically with the rest and presents characteristics of an open complex system. Because of this, cognitive function can be regarded as a result of multiple systems and subsystems interactions, while cognitive dysfunction can be seen as a result of altered interactions. From this perspective, cognitive function represents more than neural connectivity—it implies the interaction between neural networks and other network types, namely the following: gene, protein interactions, metabolic, and neurotransmitters' or neurotrophic factors' network; all organized in a "broadcasted neuroconnectomics" [2]. Additionally, all three levels of brain organization present homeostatic mechanisms that can be regarded as a dynamic interplay between different anticorrelated processes. From this point of view, cognitive dysfunction can be regarded as the imbalance of the interplay between anticorrelated processes that characterize neural connectivity, such as synchronization-desynchronization, integration-segregation, stability-flexibility, and order-chaos.

According to these concepts, this paper is organized into three parts:

1 Cognitive function as the result of multiple systems and subsystems interaction, in which the traditional reductionist approach of cognitive function is presented in opposition with the open systems approach. The philosophical theory of "holarchy," along with the more recently introduced managerial term of "holacracy," is further presented as examples for different systems' organization.
2 Cognitive function as the result of neural connectivity, presented as dynamic system interplay between different

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anticorrelated processes. This section describes the complex network theory in the framework of critical brain hypothesis.

3 Cognitive function as the result of brain connectivity, which is based on the previously described theory of the interplay between molecular/cellular level, local circuits' level, and large-scale network level. This section describes the interaction between neuronal networks and the other types of networks, with the derived implications upon cognitive function.

Cognitive function as a result of multiple systems and subsystems interaction

According to Urlic Neisser, often viewed as the founder of cognitive psychology, cognition represents a dynamic process that "involves all mechanisms by which sensory input is transformed, reduced, elaborated, stored, recovered, and used" [3]. Still influenced by the reductionist approach developed by René Descartes in the seventeenth century—reducing a system into its constitutive elements—cognitive psychology commonly analyzes the underlying cognitive processes independently: memory, attention, and executive function, along with their subdomains. However, general tendencies towards incorporating this classical view into a more holistic approach are particularly prominent in cognitive neuroscience research. Systems biology was first developed by von Bertalanffy in 1972 to study the interactions between different components of biological systems. Born as an antithesis to reductionism and behaviorism, general systems theory (GST) was based on the Aristotelean view that "*the whole is something over and above its parts and not just the sum of them all*". This concept, briefly defined as *emergence*, together with other phenomena such as *non-linearity*, *self-organization*, and *universality*, is considered to be the main property of complex systems [4, 5].

Another holistic approach, this time in more philosophical terms, but complementary to systems biology, was described by Arthur Koestler in the book "*The Ghost in the Machine*" [6]. In Koestler's view, holons are all units of a system characterized by dual behavior—they act both as autonomous individuals and as part of a more complex structure. They are organized in a multi-level holarchy, generated by their vertical interactions with super- and sub-systems components, and horizontal interactions with other parallel systems. The vertical interactions imply control by superordinate units, but, differently from the classical reductionist approach, bottom-up influences are also recognized. Holacracy, derived from the term of holarchy, is a new concept developed in management, which implies self-organization and decentralized management [7, 8].

In complex network theory—a framework for the study of systems biology—both types of organization, hierarchical and self-organization, are recognized [9, 10]. Currently, the terms of top-down and bottom-up "modulation" are preferred to "control," and there is a highlight on the dynamics of the constitutive horizontal processes/ interactions [11, 12].

The brain is considered to be characterized by a hierarchical structure with three levels of organization: the cellular and molecular level, the circuitry level, and the large-scale network level, all of which are implicated both in maintaining endogenous homeostasis and in pathophysiological processes [13]. These levels are inter-correlated; alterations that directly affect the cellular and molecular level also affect the circuitry and dynamic network levels and vice versa (Fig. 1).

In cognition, contrasting with the initial theory of independent dynamical processes, there is continuous coordination and switch between multiple sub-processes of the memory, attention, and executive function, modulated by mind wandering and metacognition. Metacognition is related to "awareness, understanding, control and manipulation of the individual cognitive processes," or briefly, cognition about cognition. It has been associated with conscious, reflective awareness which helps individuals to adapt their perception, cognitive processes, and behavior in order to improve performance [14–16]. Apparently anticorrelated with metacognition, mind-wandering or self-generated thoughts represent the shifting of attention from external or internal tasks to unrelated thoughts and feelings. Far from being just a flow of undirected ruminations, mind wandering has an indispensable role in autobiographical planning, creative problem solving, and spontaneously monitoring of own thoughts. By this impact upon cognitive processes, mind wandering is of great importance for both consciousness and flexibility of cognition, being in a dynamic interplay with metacognitive activity [17–21]. Behind the interconnections between all cognitive processes and their subdomains, there is also an intimate intertwinement with other information processing systems, such as perception, emotions, and language (Fig. 2).

Cognitive function as a result of neural connectivity—a dynamic system interplay between different anticorrelated processes

It has been generally accepted that critical dynamics is a fundamental characteristic of the brain's behavior. In other words, neurons and networks operate near a critical point, in between a phase where the activity is enhanced (supercritical phase) and a phase where activity collapses (subcritical phase). Subcritical phases are characterized by strong coordination between systemic elements in the absence of fluctuations, in which neural assemblies are locked into fixed interactions. Supercritical phases are characterized by chaotic fluctuations

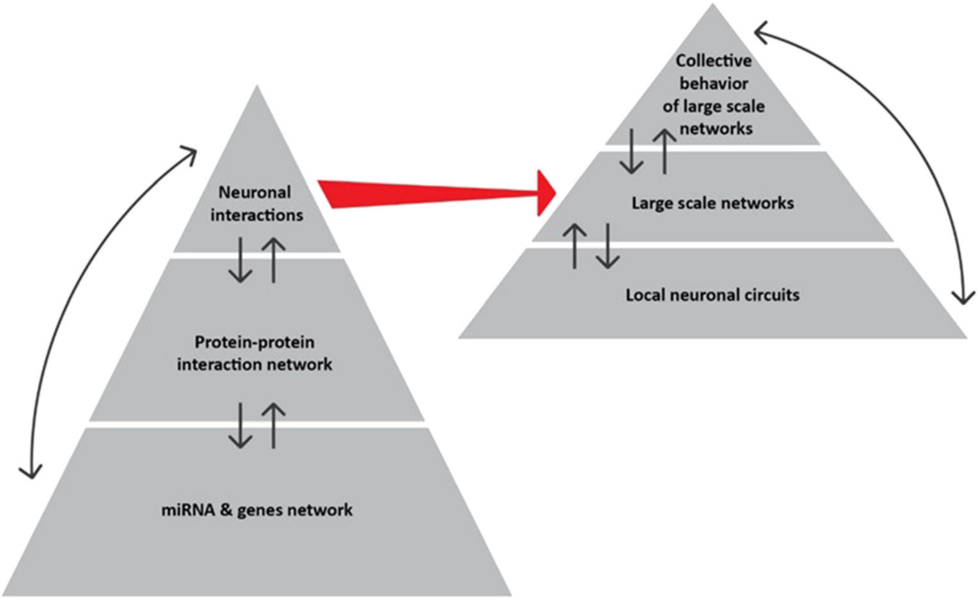

Fig. 1 Hierarchization and interdependencies of sublevels of the brain's structural and functional organization

with low coordination, which leads to a lack of stability. Operating under criticality means optimal information processing with a balance between stability and flexibility, order and chaos, synchronization, and desynchronization [22, 23]. The interplay between all these anticorrelated processes is possible through a hight complexity of processes such as:

i Reciprocal interaction of antagonistic feedback loops between excitatory and inhibitory synapses [24] that lead to cyclic oscillations in neuronal excitability.

j Wide spectrum on interneuronal communication. Behind chemical synapses, there are also electrical synapses through neural gap junction and membrane nanotubes, and a direct effect of the endogenous magnetic field upon neuronal signalling has been recognized [25, 26]. The mixture between chemical (slower, but more versatile) and electrical synapses (faster) leads to a mixture of synchronized and unsynchronized neuronal populations, generally known as *chimaera state* [27, 28].

k The coexistence of oscillatory and non-oscillatory activity. The arrhythmic fluctuations are not characterized by a temporal pattern and are usually referred to as free-scale neural dynamics. Neural avalanches represent one example of free-activity. They consist of bursts of neural activity that coexists and cooperates with oscillatory activity, being essential for the maintenance of critical dynamics [29], especially related to synchronization-desynchronization interplay [30].

As in the case of criticality, metastability is a behavior that characterizes both neuronal population/local circuits and long-range connections. It represents a balance between two anticorrelated tendencies: informational segregation and integration, or explained at length, "individualist tendencies for the diverse regions of the brain to express themselves coexist

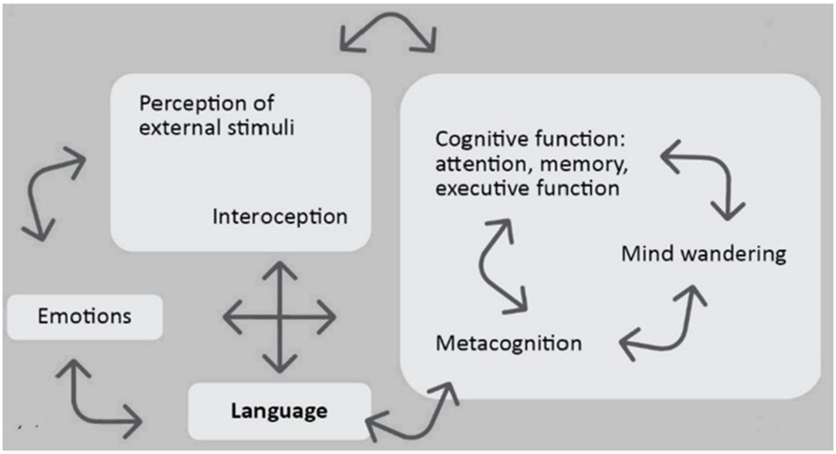

Fig. 2 Crass-talk between information processing systems. All cognitive processess are in a dynamic relathioship with each other and with the other information processing systems, such as language, perception, and emotions

with coordinative tendencies to couple and cooperate as a whole" [31].

Multistable behavior is closely linked with the notion of attractor, which is a relatively stable state towards which a system will converge—for example, a specific oscillatory pattern from a set of initial coordinates. Due to the dynamical changes in synchronization, neuronal populations are characterized by multiple attractors. The multistability represents the capacity of a system to jump from a partially synchronized state to another, known as metastable states, leading to a heterogeneous synchronization pattern [32].

Synchronization-desynchronization interplay

The continuous switch between synchronization-desynchronization has been recognized in each level of the brain's organization, being a bilateral influence between local neural dynamics and large-scale networks. At the level of neuronal populations and microcircuits, it is the direct result of the mechanisms described above—the balance between excitatory and inhibitory microcircuits, the delays between different types of neuronal synapses, and the coexistence between oscillatory and non-oscillatory neuronal activities. At the level of large-scale structures, it is also influenced by coherence and entrainment between the oscillatory activity of different brain regions.

Synchronization-desynchronization interplay is indispensable for the network's adaptability and depends on networks' functional and structural integrity. As a system gets imbalanced—structural and functional alterations due to trauma, neurodegenerative processes, ionic channels, or neurotransmitters' imbalances—it moves away from the edge of criticality. This act triggers an imbalance between synchronization and desynchronization translated into a mixture between hypo and hyperconnectivity, as observed in a wide spectrum of neurological and psychiatric pathologies—vascular or Alzheimer's dementia, Parkinson's disease, epilepsy, autism spectrum disorders, and schizophrenia.

The structural connectome has been defined as a complex map of neural connections, in which nodes correspond to grey matter assemblies and edges correspond to structural white matter pathways that are located in between them (Box 1) [33].

Box 1 Graph theory applied to neural networks

First developed in the 18th century by Leonhard Euler, graph theory provides a practical mathematical framework for studying relationships. It is broadly used in neuroscience in both structural and functional studies of brain's network.

➢ Nodes may represent either individual neurons or, more often, interconnected brain regions. In fMRI studies, they represent regions of interest (ROI) – the parcellation of the original voxel-level data, in electroencephalographic (EEG) they represent electrodes' position, and in magnetoencephalographic (MEG) sensors' position.

➢ Edges may represent either a structural or functional relationship between the nodes.

➢ Degree distribution K of a node represents the number of direct connections of that node. The average degree distribution of a network represents the average of the degrees of all nodes and represents a measurement of the connectivity of that network.

➢ Betweenness centrality represents the number of times a node acts as the strongest connecter between any two different nodes.

➢ Participation index measures the distribution degree of a node among all modules.

➢ Shortest path length represents the smallest number of edges between two given nodes.

➢ Clusters are groups of interconnected nodes.

➢ Clustering coefficient represent the ratio between the number of edges among neighbours of a node and the maximum number of edges among those neighbours.

➢ Hubs are nodes with a higher influence on the network's dynamics because of higher degree distribution, betweenness centrality and participation index.

➢ Modularity represents the characteristic of brain's network to be organized in distinct functional networks communities. It has an essential role in the integration-segregation interplay. Modules are interconnected through hub nodes.

➢ Small worldness represents the type of the complex networks that combines short path length between regions of interest (increased global efficiency) and an increased clustering coefficient. Other types of networks are represented by the Random Graph of Erdos and Rényi and Scale-free Networks of Barabási and Albert (Fig. 3). Small wordness and/or free-scale networks are conferring the optimal efficiency and resilience of neural networks.

➢ Rich club organization represents the tendency of the hubs with high clustering coefficient to connect within themselves [33].

Computational models of large-scale resting-state networks (RSN) suggest that the nodes of a network, as well as the clusters, are characterized by a high level of synchrony. In contrast, the global network is partially asynchronous due to time-delay interactions [34]. The strength of correlations inside a node, cluster, or network varies in time, with periods of strong correlations alternating with periods of partial synchronicity or asynchronicity [35]. A specific task determines simultaneous phase modulation and synchronization of task-relevant brain regions. This translates into enhanced connectivity, but with high energetic costs [36, 37], rendering vulnerability of nodes with a higher clustering coefficient in pathologies associated with mitochondrial dysfunction: neurodegenerative diseases, stroke, traumatic brain injury, epilepsy, and others.

An example of how structural lesions can have an impact on connectome dynamics are patients with diffuse axonal injury caused by traumatic brain injury (TBI). In their case, an altered integration of sensory, motor, and cognitive information was observed, with a reduction in metastability of RSN. This was associated with both increased and decreased interconnectivity and altered cognitive functions (e.g., reduced cognitive flexibility, information processing, and associative memory) [38].

Segregation-integration interplay

The connectome is characterized by both segregation and integration of neuronal information. The modular organization (clusters) is responsible for segregation and specialization, while network hubs are responsible for integration [39, 40]. Small-world organization, which combines short path length between regions of interest (increased global efficiency) and an increased clustering coefficient, is considered to be optimal for functional cognitive status (Fig. 3; Box 1). It is a balanced trade-off between minimizing the energetic wiring costs and maximizing information processing [41, 42].

As previously discussed on the synchronization-desynchronization balance, the dysfunction or loss of nodes with a high degree in connectivity also disrupts the "small-world" organization, leading to a reduced number of long-range connections, increased clustering, and path length [37, 44–46]. It appears that lesions that affect central nodes with a high participant coefficient lead to an increase in metastability. Lesions that affect peripheral nodes, with lower participant coefficient, lead to a decrease in metastability [47]. The result is a mixture between decreased specialization and global integration and an intra-network hyperconnectivity, with less capacity of dynamical reorganization and reduced variety of neural states. These are crucial for cognitive processes, such as inhibitory control [48–52]. Loss of small-world state was observed in MCI patients both during active and resting state and is considered to be a reliable biomarker for the progression of cognitive dysfunction [53, 54]. All brain functions, especially cognition, imply a dynamic balance between segregation and integration that results in a perpetual functional and structural reorganization of the brain. Such a dynamic balance was intensively studied between resting-state networks (RSN), characterized by spontaneous activity that increases in the absence of a task, and task-positive networks (TPN) (Box 2) [42 55–58] . The segregation between RSN and TPN networks is relative. Recent studies have highlighted that parts or RSN and TPN may be activated together and promote each other. For example, although default mode network (DMN) is considered to function in opposition to the salience network (SN) [59], parts of DMN are activated along with task-activated regions during cognitive activities: ventral posterior cingulate cortex during attention-demanding tasks [60], inferior parietal cortex [61], medial prefrontal cortex, and posterior cingulate cortex [62] during preparation and retrieval phases of working memory and also inferior parietal cortex during error awareness (a metacognitive ability) [63]. Moreover, mind wandering is not only associated with increased activity of DMN, but also with decreased connectivity in different regions within this network. This probably occurs as a consequence of coactivation during novel tasks [64].

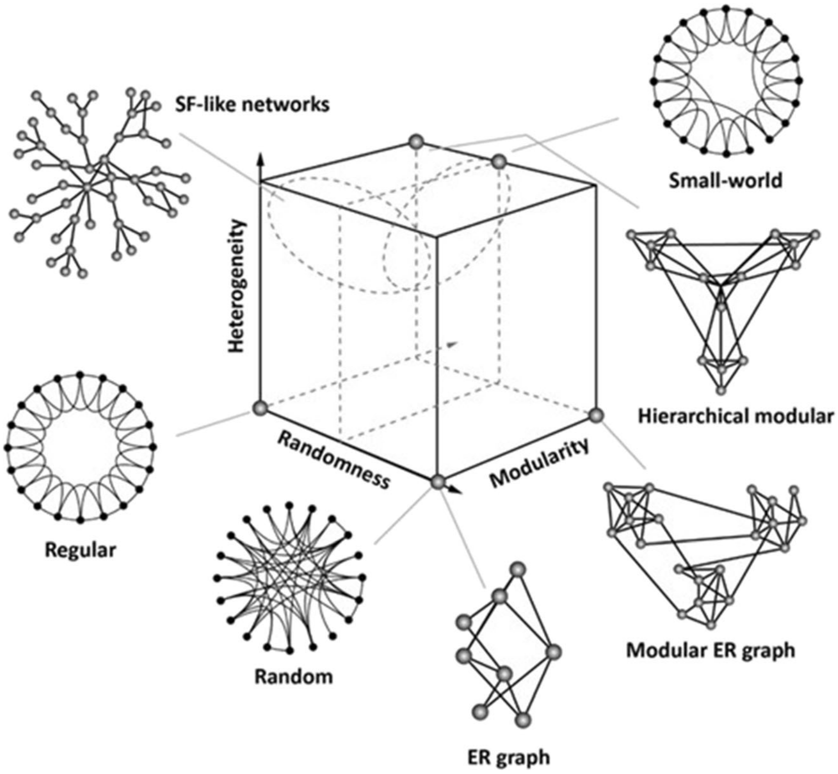

Fig. 3 Different types of complex networks (regular, random, ER graph, modular ER graph, hierarchical modular, small-world, and SF-like networks). Adapted after Solé RV et al. [43]

Box 2 Resting-state and task-positive networks

Traditionally, brain networks have been divided into resting- state (RSN) and task-positive networks (TPN).

The most important RSM is the default mode network (DMN). It uses the most direct structural connection from the all RSN, involving precuneus, posterior cingulate (retrosplenial cortex), ventromedial prefrontal cortex, inferior parietal lobes (angular gyrus) and lateral temporal cortex [42, 55].

Examples of TPN networks include salience network (SN), central executive network (CEN), attention networks (DAN and VAN) and motor network (MOT). SN is activated by external stimuli and contains dorsal anterior cingulate and frontoinsular cortexes. CEN is activated by cognitive tasks and is composed by the dorsolateral prefrontal cortex and the posterior parietal cortex. The DAN (dorsal fronto-parietal network) is responsible for both top-down and bottom-up types of attention, while the VAN (ventral fronto-parietal network) is predominantly responsible for bottom-up attention; these two networks function through dynamic interaction. MOT includes the bilateral primary network cortex, a part of the bilateral primary somatosensory cortex and the supplementary motor area [56–58].

In addition to an overlap in the activation of RSN and TPN, networks that were initially considered to be pure TPN are also activated in the absence of task-relevant stimuli. Examples of such networks are ventral attention network (VAN) and motor network (MOT) [35, 65, 66]. DMN, along with VAN and MOT, achieve the integration of internal cognitive processes with sensory and motor information through several hubs characterized by rich-club organization. These processes are otherwise segregated [67]. In order to achieve this dynamic, the hubs actively change the degree of connectivity, switching their roles in a network from high centrality to low centrality and vice versa [55].

Through this "dynamic core," RSN presents a dynamic behavior, continuously coupling and decoupling to optimize the global flow of interaction.

It is increasingly recognized that focal lesions, such as those encountered in stoke, do not determine isolated deficits linked directly to the injured areas, but rather correlated cognitive-behavioral phenotypes that result from an overall imbalance of the whole connectivity. Structural changes, such as an increase of the shortest path length between two regions indirectly connected, were associated with functional connectivity alterations that are derived from a reduction of modularity and an imbalance of segregation-integration interplays [68, 69].

Stability-flexibility interplay of informational flow

The analysis of the collective behavior of large-scale networks, independent of methodology, is based on the idea of emergence—the property of a system to be much more than its compounds. The challenge consists in analyzing patterns of interaction between multi-level temporal and spatial activities. For example, parts RSN can change connections across time, recombining into different networks with a completely new behavioral phenotype. The dynamics of these recombinations depends on both internal and external events, giving rise to a broad variety of functions [70]. In physiological condition, this adaptive behavior is governed by a balance between deep and shallow attractor basins. The first one is associated with robustness of informational flow, and the second one with high variability. Too much robustness leads to a decrease in networks' dynamics, by trapping the oscillations into fix patterns. In terms of cognitive function, it translates into the difficulty of the attentional switch from one task to another or less receptiveness to different stimuli, phenomenon encountered in specific phenotypes of autism spectrum disorder and depression. It can also be translated into chronic, stable maladaptive reorganization that occurs after structural lesions, such as in stroke, or into pathological hyperconnectivity states encountered in seizures. Shallow basin attractors are associated with weak synchronization and frequent shifts of transition states, which may lead to difficulty in maintaining attention on one task, as in the case of attention deficit hyperactivity disorder (ADHD) [71].

Order-chaos interplay: from signal complexity to temporospatial variability

The complexity of the brain's behavior derives both from non-oscillatory neural activity and oscillatory temporospatial dynamics of large-scale networks.

For an extended period, the free-scale neural activity was considered to be just noise and hence removed from many EEG and local field potential (LFP) studies due to emphasis of oscillatory frequency [72, 73]. It was highlighted by BOLD (blood oxygenation level-dependent) signal of functional magnetic resonance imaging (fMRI) as spontaneous fluctuations occurring at a slow frequency (< 0.1 Hz) [74, 75], by EEG and MEG studies as a complex combination between multiple frequency bands, between 8 and 30 Hz [76–78], and by LFP studies as variating between 50 and 150 Hz [79]. Currently, it is considered to be essential for maintaining the dynamics and flexibility of neural firing patterns, as it facilitates transitions between different oscillatory patterns, helps neurons to reach a firing threshold, and keeps a balance between neuronal synchronization and desynchronization [80]. Changes in fractal dimension were observed in different neurological and psychiatrically disorders, decreasing in stroke [81], vascular and Alzheimer's dementia [82, 83], and in schizophrenia [84], and increasing in depression [85]. An increased signal complexity was also found during seizures, and a decreased complexity, in interictal periods [86].

Similar to the neural free-scale activity, the complexity of the temporospatial dynamics of large-scale networks has the role of facilitating the transition between different alternative brain states. A standard measure of the complexity of the dynamical connectivity is entropy, which measures both variability and diversity of the neural states' repertoire. Changes in entropy were linked with both structural and functional alterations of connectivity. For example, in post-stroke patients, loss of the degree of the nodes was correlated with lower entropy, both on the lesioned and contralateral side [87]. Altered functional connectivity (FC) of DMN between posterior cingulate cortex and right hippocampus in Alzheimer's dementia patients was associated with both a reduction in multi-scale entropy (MSE) and cognitive performances [88]. In contrast to structural connectivity, FC has been considered to be variable in both time and space, linking different connectivity states between different neural systems [89]. Additionally, recent studies suggest that MSE and FC represent two sides of the same coin, both of them assessing the complexity of information processing [90, 91].

Cognitive function as a result of brain connectivity

Brain connectivity represents much more than neural connectivity. The dynamics of neural networks are directly influenced by the interferences of other types of networks: gene networks, protein interaction networks, metabolic networks, neurotransmitters' network, neurotrophic factors' network, and many others.

It is well known that the brain's network strength is modulated by synaptic communication, namely long-term potentiation (LTP) and long-term depression (LTD), and by resting membrane potential. These are determined by the expression of genes closely linked to neurotransmitters and ion channel activity. Recent studies have proven the association between functional networks (including resting-state networks) and gene networks, with direct implications on neuro-psychiatric pathologies [92–94]. Moreover, neurodegenerative diseases, such as Alzheimer's disease (AD), appear to be correlated with the accumulation of functional genetic alterations inside the entire genetic network, rather than punctual, independent mutations [95, 96]. The notion of gene networks is derived from the observation of dynamical regulatory interactions between genes. Similar to brain networks, gene networks are characterized by both robustness and sensitivity, oscillatory and non-oscillatory, free-scale activity [97–99].

Synchronization of neurons by temporal coordination during gamma oscillations is modulated by the interplay between inhibitory and excitatory neurotransmitters. gamma-Aminobutyric acid (GABA) levels have been proved to modulate RSN. High GABA concentrations in the posterior cingulate cortex and precuneus are associated with DMN deactivation, which is essential in the proper performance of task-related activities [100]. Moreover, GABA is involved in the modulation of the basal ganglia network, cortico-striatal connectivity, and thalamo-striatal connectivity. These play important roles in the executive function [101, 102]. However, the function of inhibitory fast-spiking interneurons, which are responsible for the release of GABA [103], is dependent on high energy expenditure, rendering neurons vulnerable in the elderly and individuals with various neurologic pathologies (e.g., neurodegenerative diseases, stroke, and vascular dementia) [104]. Overexpression of glutamate signalling in AD [94] contributes to the imbalance of neurotransmitters, with subsequent alteration of synchronization in different frequency bands [105] and with alteration of large-scale networks [106, 107].

A fascinating consequence of the interferences between neural activity and the other types of networks is the potential of changing pathological pathways by applying different types of brain stimulation. For example, gamma frequency entrainment induced by sensory stimuli generates changes in microcirculation, microglial activation, and facilitates amyloid load reduction in mouse models of Alzheimer's disease [108]. High-frequency repetitive transcranial stimulation (rTMS) interacts with genes involved in neuroprotection pathways and modulates astrocyte activity [109]. There is still need of research for understanding how to find ways to interact with all this complexity of intricated systems and subsystems, but all the advances that have already been done in the understanding of brain's dynamics have brought us closer to new treatment opportunities for patients with cognitive impairment.

Concluding remarks

According to Maurizio Corbetta, "*the function of any brain region or its dysfunction after damage cannot be understood in isolation but only in conjunction with that of other connected regions, and by considering not only how a region responds to stimuli or tasks, but its spontaneous activity and its interactions with other parts of the network.*" In agreement with this vision, we assert that cognitive dysfunction represents a consequence of a global imbalance of all three levels of brain organization: cellular and molecular level, circuitry level, and large-scale network level. Even more, at all these levels, dysfunctions can be translated as an imbalance of the interplay of anticorrelated processes which maintain the critical dynamics of the brain's function under physiological conditions. It is also important to remember that the central nervous system is bidirectionally related with other fundamental systems such as the immune, endocrine, and autonomic systems, and microbiota, all of which present changes in patients with cognitive dysfunctions.

We conclude that therapeutic approaches for cognitive dysfunction targeting isolated components of a system that presents imbalance are ineffective and should be considered with caution. Neurocognitive disorders require a combination of synergistic interventions, starting with clinical observations, tracking of potential systemic imbalances, and employing an iterative tailoring process, based on the clinical evolution of individual patients.

Authors' contribution CB and DS conceived the idea of the manuscript. CB, DS, and MB were involved in writing the manuscript. DS, LPL, and ES performed the literature search. DFM and SS critically revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies involving human participants performed by any of the authors.

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