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On the connectivity in the central nervous system and the age-induced changes of its network organization

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Abstract. Intercellular communication plays a crucial role as the structural substrate for the brain functions. It occurs according to two main processes, namely wiring transmission, i.e. the transmission of signals through physical contacts between cells, and volume transmission, i.e. the chemical signal diffusion along the interstitial fluid pathways. Intercellular communication represents the main rationale for the emerging field of connectomics, defined as the comprehensive study of all aspects of central nervous system connectivity, aimed at creating a comprehensive map (connectome) of the cellular networks in the brain to better understand brain functions. A consensus exists that the brain connectome structure follows a hierarchical or nested architecture, and macro-, meso- and microscales have been defined. Available data on network organization at these different miniaturization levels will be here briefly reviewed. The connectome, however, is also a dynamical entity, undergoing changes during lifetime. Thus, a specific focus will be maintained on the changes the network organization undergoes during normal aging.

Keywords: intercellular communication, brain networks, brain aging, connectome, molecular networks.

INTRODUCTION

The central nervous system (CNS) can be well described as an interaction-dominant dynamics system (Anderson et al., 2012; Guidolin et al., 2017) where interaction processes among cells and regions determine virtually all aspects of its integrative function, making difficult, and sometimes impossible, to assign tightly defined and unique roles to each specific component. The key role played by the network architecture as a structural substrate for the CNS functions represents the main rationale for the emerging field of connectomics, the comprehensive study of all aspects of CNS connectivity (Sporns, 2012). This idea has a quite long history behind it (see Schmahmann

and Pandya, 2007). Early neuroanatomists, indeed, were aware of the inappropriateness of their anatomical techniques to unravel the complex brain organization, and mapping the connections within the CNS has been a scientific goal for centuries. A significant example is represented by the 1685 Steno's far-sighted lecture "On the anatomy of the brain" (see Steno, 1965) where he emphasized the need of a program aimed at detailing brain anatomy in particular for what it concerns the fibers course through the white matter, since "it is impossible to explain the movements of a machine if the contrivance of its parts is unknown".

The characterization of inter-neuronal pathways, however, became possible only when new methods able to stain and trace neuronal connections were developed (Flechsig, 1901; see Sporns, 2013, for a thoughtful historical summary on this topic), and a significant advancement in the field occurred in the 1990s with the development of noninvasive magnetic resonance-based imaging methods and the related computational techniques (see Le Bihan and Johansen-Berg, 2011, for a review). Thus, the idea emerged of creating a comprehensive map of the brain structural connections to better understand brain function based on the structural features of neuronal networks, leading to the definition of the NIH 'Human connectome project' (www.humanconnectomeproject.org) aimed at providing an unparalleled compilation of neural data and the opportunity to achieve never realized conclusions about the living human brain (Van Essen et al., 2012). As pointed out by Sporns (2013), the emphasis on structure is important because anatomically determined connections among CNS elements embody a large (but finite) set of properties that (at least in principle) can be objectively mapped and represented by appropriate network models characterized by well-defined geometrical, biophysical and functional features. Defining the connectome, however, involves a careful analysis of the communication processes existing between CNS elements and of the pathways they exploit.

In this respect, it has to be observed that although networks of neurons interconnected by synapses represent the fundamental structural substrate of the CNS function, they do not deal exhaustively with the issue. In the last decades, indeed, a broadened view on the connectivity in the CNS came with the proposal (Agnati et al., 1986; Nicholson, 2001) of the existence of two main modes of intercellular communication in the CNS (see Guidolin et al., 2017 for a recent review), that have been called wiring transmission (WT: point-to-point communication via private channels, as, for instance, synaptic transmission) and volume transmission (VT: communication by diffusion in the extracellular fluid and in the cerebrospinal fluid). Experimental evidence suggested that these communication processes involve not only neurons but also other types of cells in the CNS (Syková and Chvátal, 2000; Färber and Kettenmann, 2005; Guidolin et al., 2022), allowing the formation of 'complex cellular networks' including neurons and glial cells (in particular astrocytes), in addition to the extracellular matrix.

A further aspect deserving consideration concerns the hierarchical structure exhibited by CNS networks. It is well known, indeed, that all anatomic systems exhibit the pivotal property to form multiscale structures (Jacob, 1970) each of which forms "a whole in relation to its parts and is simultaneously part of a larger whole" (Grizzi and Chiriva-Internati, 2005). In the CNS this feature is of particular relevance, being its architecture extending over a range of up to five orders of magnitude of scales: from microns for cell structures at one end to centimeters for inter-areal neuronal connections at the other. Thus, a hierarchical or nested architecture has been suggested as a suitable model to describe the CNS network organization (Agnati and Fuxe, 1984; Sporns et al., 2005; Sporns, 2013; Guidolin et al., 2016). From the point of view of connectomics this structural feature poses a significant challenge (see Zalesky et al., 2010), that concerns an unambiguous identification of the significant levels of organization. In this respect, an almost general consensus exists (see Agnati and Fuxe, 1984; Sporns et al., 2005) in defining at least three nested levels (see Guidolin et al., 2017 for details), namely the "macroscale" (where CNS areas and neuronal populations represent the basic elements), the "mesoscale" (the level of complex cellular networks forming a CNS area) and the "microscale" (where single cells and intercellular contacts, such as synapses, can be found). They are schematically illustrated in Figure 1 and briefly discussed in the sections that follow. Furthermore, being age one of the arguably most robust sources of neurobiological variation in the connectome, a specific focus will be on available data illustrating the changes the CNS network organization undergoes during normal aging.

MACROSCALE: CNS NETWORKS AND PATHWAYS

Basic elements at this level are CNS areas, neuronal populations and the pathways connecting them. A number of anatomical regions on the order of 100 or more (Van Essen et al., 1998; Glasser et al., 2016), for instance, can be defined in the human cerebral cortex on the basis of several different criteria (see Wig et al., 2011). Despite the limitation associated with the lack of

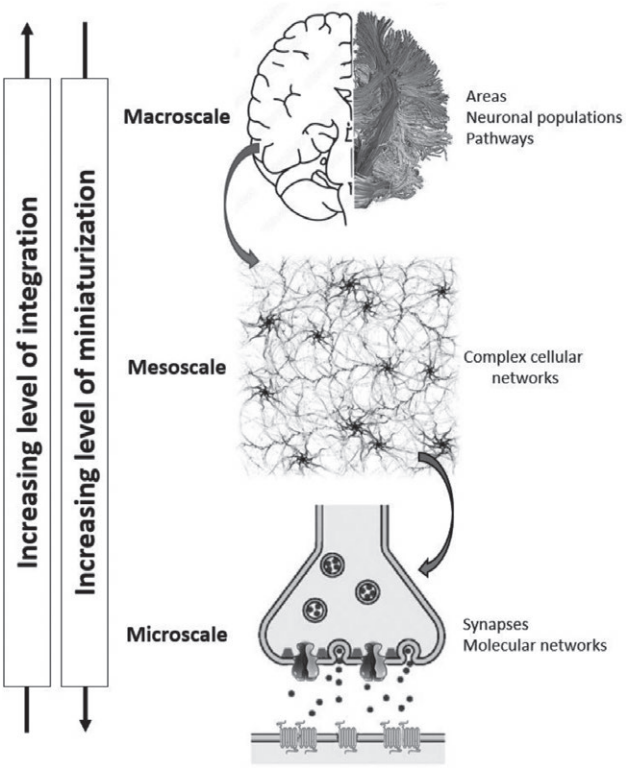

Figure 1. Schematic representation of the hierarchic structure of CNS networks, characterized by at least three nested levels of increasing miniaturization.

a single universally accepted parcellation scheme, the macroscale level is considered the most feasible organizational level for a first draft of a connectome (Sporns et al., 2005). In this respect, direct, invasive, techniques for localizing brain regions and tracing anatomical connections have been available for many decades and used in animal studies. They involve the use of tracers and the post-mortem analysis of the distribution of labeled axons (Markov et al., 2011). For mapping neuronal connections non-invasively in the human brain two approaches are currently used (see Behrens and Sporns, 2012), both involving magnetic resonance imaging (MRI), but relying on very different principles. 'Diffusion tractography' (tMRI) aims to infer the tracks of axon bundles in the white matter, while 'resting state functional MRI' (rfMRI) measures spontaneous fluctuations in the blood-oxygenation-level-dependent (BOLD) signal in grey matter regions and estimates statistical dependencies between these time series. Although methodological issues (see Behrens and Sporns, 2012; Mohanty et al., 2020), such as reduction of artifacts and improvement of accuracy by using more appropriate metrics, still deserve further development, the analysis by methods from network science and graph-theory (Rubinov and Sporns, 2010; Fornito et al., 2013) of available MRI datasets obtained in animals (see Hilgetag et al., 2000) and humans revealed a convergence on some key features of brain architecture. Concerning the neural connections between different cortical areas, for instance, they were shown to possess an organization in the form of 'small-world networks' (Watts and Strogatz, 1998; Liao et al., 2017), characterized by clusters of nearby cortical areas connected by short links, which in turn have long-range connections to other clusters (Sporns and Zwi, 2004; Stam and Reijneveld, 2007). Within clusters, the network topology identified by functional MRI is the type called 'scale-free' (Eguiluz et al., 2005), in which some nodes (hubs of connectivity) have a high number of connections to other nodes, whereas most nodes have just a handful. These basic architectures are schematically illustrated in Figure 2. VT pathways at macroscale were also proposed (see Fuxe et al., 2013; Illes, 2018). The proposal was based on the hypothesis that cyclic pressure oscillations (associated to intracranial arterial pulses) exist in the subarachnoid space leading to "tide" movements (Agnati et al., 2005) in the fluid of the Virchow-Robin spaces. Such convective movements would generate long-distance VT signals (Picard and Zanardi, 2015). As indicated by experimental studies on β-endorphin (Bjelke and Fuxe, 1993; MacMillan et al., 1998), peptidergic neurons appear able to operate via long-distance VT with distances in the range of millimeters (Jansson et al., 2002).

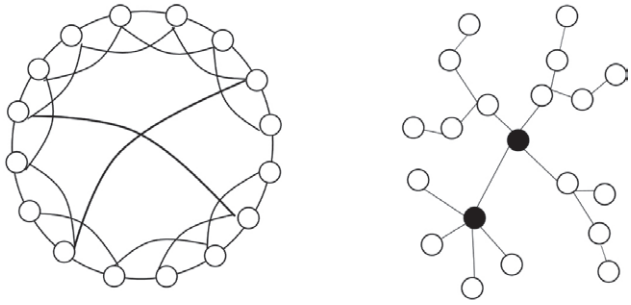

Figure 2. Schematic representation of the two basic network topologies identified in the CNS. The left panel illustrates a 'small-world network' and the right panel a 'scale-free network' (see text for details).

This research effort provided important insights into how anatomical connections shape and constrain brain dynamics, how this relation varies across individuals, and applications to clinical disorders are under development (Siddiqi et al., 2023). Concerning MRI-based life span studies (see Zuo et al., 2017 for a detailed review on the topic), tMRI approaches largely confirmed early findings indicating an inverted-U trajectory for white matter

development (Mwangi et al., 2013). In particular, phylogenetically primitive sensorimotor brain structures were found to exhibit the most rapid development and greatest preservation, while more phylogenetically advanced structures (e.g., prefrontal cortex) showed slower development and faster declines, suggesting a first-in-last-out pattern of development across the life span (Imperati et al., 2011). Complementing structural perspectives of life span development for the connectome are those emerging from rfMRI, suggesting, in young brains, age-related increases in long-range connectivity when compared to both short-range and interhemispheric connectivity (Fair et al., 2007). By contrast, aging studies revealed consistent patterns of decreases in long-range connectivity (Andrews-Hanna et al., 2007), leading to a reduction in network modularity (Chen et al., 2011; Varangis et al., 2019), i.e. in the propensity for a network to be divisible in subnetworks or modules. The interpretation of this pattern of results is contentious, with some suggesting that this pattern represents a compensatory process which allows an optimization of the wiring cost in older adults (Cabeza, 2002), while others posit that it simply reflects network dedifferentiation (Colcombe et al., 2005), a process that could be associated with some decline of cognitive functions (Varangis et al., 2019).

MESOSCALE: COMPLEX CELLULAR NETWORKS

Within each brain region, segregated neuronal subcircuits can be recognized. A classic example is provided by cortical columns (Lorente de Nò, 1938) consisting of an array of cooperating neuronal groups extending radially across the cortical layers and representing units of operation (Rakic, 2008). They appear loosely delimitated in morphological terms, being dynamic entities changing according to functional needs. A role in delimiting them is probably played by astrocytes, since the astroglial cells, especially in mammalian brains, define the microarchitecture of the parenchyma by dividing the gray matter into relatively independent structural units through a process known as 'tiling' (Bushong et al., 2004).

The relationship between neurons and astrocytes, however, is much more significant than this (see Guidolin et al., 2023 for a recent review). Evidence, indeed, exists highlighting the involvement of 'neuron-astroglial interactions' in the higher brain functions (Pereira and Furlan, 2010). As a matter of fact, the concept of 'tripartite synapse' has been introduced (Araque et al., 1999), since in most glutamatergic central synapses, the extremity of a protoplasmic astrocyte process wraps the synaptic cleft. Since astrocytes express membrane receptors to neurotransmitters and can release their own chemical messengers (gliotransmitters), this arrangement allows them to establish a cross-talk with both pre- and postsynaptic neurons. Several astrocytes participate in this functional organization, coupled with each other by gap junctions, leading to the formation of real neuroastroglial networks (Fellin and Carmignoto, 2004).

A further broadening of this view can be appreciated when VT-based intercellular communication processes are considered. In fact, this signaling backbone involves almost all the types of cells in the CNS (Syková and Chvátal, 2000). Hence, the concept of 'complex cellular networks' has been introduced to indicate the set of cells of any type that exchanging signals in a certain volume of brain tissue are capable not only of integrating multiple inputs to give out appropriate outputs but also of supporting each other's survival (Agnati et al., 2000).

On this basis, it can be proposed that the basic network elements at mesoscale should be defined by considering not only neuronal networks but also whole compartments of brain tissue where different cell types and the extracellular matrix work as an integrated 'functional module' (Agnati et al., 2009; Guidolin et al., 2017).

Age-related changes in brain cell number received a significant attention in the last century. Early studies (reviewed in Pannese, 2011) led to the idea that a significant loss of neurons occurred during normal aging, suggesting such a substantial loss as the origin of the cognitive decline often associated with brain aging. However, subsequent studies (see von Bartheld, 2018; Pannese, 2011 for reviews), exploiting more accurate morphometric methods, have evidenced that during normal aging neuronal loss is limited to restricted regions of the central nervous system and is quite small (probably no more than 10%). Similar concepts apply to astrocytes as well (see Pannese, 2021) and changes with aging in astrocyte number were detected only in specific brain regions. Moreover, the idea of an overabundance of glial cells as compared to neurons also changed with the development of modern counting methods and the concept that glial cells are not more abundant than neurons in human brains is now becoming increasingly accepted in the field (von Bartheld, 2018).

During aging, however, evident morphological changes have been reported in both neurons and glial cells. The most common age-related structural changes undergone by neurons involve a reduction in the complexity of dendrite arborization and dendritic length, and the myelin sheaths of axons may become less compact (Dickstein et al., 2007; Pannese 2011). Concerning glial cells, astrocytes may become hypertrophic and accumulate intermediate filaments, oligodendrocytes

and Schwann cells exhibit alterations consistent with the observed changes to the myelin sheaths, while in microglia, proliferation in response to injury, motility of cell processes, ability to migrate and phagocytic capabilities are often reduced (Rodriguez-Arellano et al., 2015; Pannese, 2021). Possible age-related modifications affecting VT processes in the cortex were also investigated (Nicholson, 2005) indicating no significant changes of the extracellular space in terms of volume and tortuosity, suggesting that, at least in the cortex, diffusion properties for small signaling molecules should not change dramatically with age.

Altogether these changes likely may modify the pattern of intercellular interactions at this scale, probably contributing to the behavioral impairment and cognitive decline often associated with normal aging.

MICROSCALE: SYNAPSES AND MOLECULAR NETWORKS

At this scale, single cells and synapses can be found. Of particular interest at this level are the so-called synaptic clusters (SC), in which multiple synapses act cooperatively to modulate their strength (Golding et al., 2002). SC are often organized around the dendritic spines and partially isolated from the surrounding environment by glial cells (Golding et al., 2002; Cutsuridis et al., 2009).

As pointed out by Sporns et al. (2005), drawing the connectome at microscale is infeasible, at least in the near future. Even considering the single neurons as the basic element, the connections to map would be in the order of 10^{15}, a technically impossible task. If we also consider other cell types and VT connections, the connectome size would become even greater. However, it must be said that such a level of structural detail may be unnecessary and a simple characterization of mechanisms remodeling connectivity at this scale could represent a sufficiently significant dataset for a deeper description of CNS functions. In particular, to better capture properties concerning the strength and plasticity of synapses, looking at the cell membrane can be useful. At this level molecular networks can be found. They are made of molecules (in particular proteins) that function as a metabolic and/or regulatory signaling pathway in a cell (Bhalla and Iyengar, 1999). For our discussion of particular interest are the 'receptor mosaics', i.e. macromolecular complexes formed at the membrane level by receptors as a consequence of direct (structural) allosteric receptor-receptor interactions (see Guidolin et al., 2019; 2023 for recent reviews). The cooperativity that emerges in the actions of orthosteric and allosteric ligands of the monomers forming the assembly provides the cell decoding apparatus with sophisticated dynamics in terms of modulation of recognition and signal transduction. Thus, the formation of the receptor mosaics allows an integration of the incoming signals already at the plasma membrane level and can significantly contribute to set and tune the efficiency of the connections between cells and, in particular, the synaptic strength (Agnati et al., 2003). Interestingly, methods from graph and network theory appear appropriate also to describe the dynamic behavior of interacting receptors (Guidolin et al., 2007), further suggesting the possibility of including these structures in the context of connectomics. In particular, the possible existence of receptors acting as 'hubs' in the receptor assembly has been suggested (Agnati et al., 2016). Due to their position in the network of receptor interactions, hub receptors could play a key role in the integrative action of the assembly and represent a target of primary importance from the pharmacological perspective.

As mentioned before, with increasing age the dendritic tree undergoes progressive regression. In this context, it has been known for a long time that the number of dendritic spines significantly decreases (Nakamura et al. 1985; Nunzi et al., 1987). These changes have been assessed quantitatively in certain regions of the nervous system. For instance, the reduction in spine number in monkey cerebral cortex ranges from 25 to 50% according to the area considered (Dumitriu et al. 2010), while in the CA1 region of the rat hippocampus the reported reduction was of about 12% (Nunzi et al., 1987). Being dendritic spines important sites of synapse formation, these findings are consistent with observations indicating a decrease of neuronal connectivity at microscale during normal aging (Morrison and Baxter, 2013). A tendency to reduced inter-astroglial coupling has also been reported (Cotrina et al., 2001). However, during aging astrocytes seem to conserve their ability to express spontaneous and neurotransmitter-dependent intracellular Ca^{2+} signals. Moreover, gliotransmission resting levels, and astrocyte-neuron interactions also appear largely conserved (Gomez-Gonzalo et al., 2017).

From the functional standpoint, one of the general hallmarks of aging is the decline of a number of physiological functions in response to a variety of stimuli. These observations led to an emerging hypothesis attributing aging to loss of cell communications (see Robert and Fulop, 2014) mainly associated either to some receptor loss in aging cells and tissues or to their uncoupling from their specific signaling pathways (Santos-Otte et al., 2019). Several examples of these processes have been

documented in the CNS. They include decline in muscarinic responsiveness with age (Joseph and Roth, 1990), loss of D_2/D_3 dopamine receptors in extrastriatal regions (Kaasinen et al., 2020), and alterations in the expression and activity of $G_{i/0}$ protein-coupled receptors in the human frontal cortex, hippocampus, substantia nigra and striatum (de Oliveira et al., 2019). The involvement of G protein coupled receptors (GPCRs) is of particular interest for the present discussion, in view of their well-documented (see Guidolin et al. 2007; 2019; 2023) capability to form receptor complexes at the cell membrane through direct allosteric receptor-receptor interactions. In fact, due to oligomerization of GPCRs at the membrane and their cooperative signaling, downregulation of some specific GPCR may affect signaling and drug targeting of other types/subtypes of GPCRs with which it interacts, opening the possibility that the dynamics of molecular networks could exhibit significant age-associated changes.

CONCLUDING REMARKS

The rapid increase of studies addressing connectomics clearly indicates that the anatomical mapping of the relationship among CNS components may lead to a deeper level of understanding of CNS functions. The CNS, indeed, is believed to accomplish its activity mainly through the integrative action of networks in which functions emerge from collections of elementary units (nodes), linked by connections and bound together dynamically (Bullmore and Sporns, 2012). Thus, drawing the connectome is much more than collecting a large descriptive dataset. It strongly implies the adoption of network models for brain function, including but not limited to the quantitative methods offered in abundance by network science (Sporns, 2013).

This research effort has been so far focused mainly on neuronal connectivity at a macroscale level, exploiting the possibilities offered by magnetic resonance imaging to evaluate the inter-regional structural and functional connectivity patterns. The obtained data demonstrated a number of nontrivial architectural features of the human neuronal networks (Behrens and Sporns, 2012). Brain integrative actions, however, strongly depend, but certainly not only, on the wiring diagram of neurons, since additional networks and processes exist modulating neuronal activity (Brezina, 2010). In this respect, two aspects should deserve consideration.

The first refers to the increasing evidence indicating that synaptic transmission is significantly complemented by cell types other than neurons. As illustrated above, neurons and glial cells form complex cellular networks communicating via two modes of connection, WT and VT, which are not mutually exclusive. From the connectomics point of view, it is also of interest to observe that both modes can be identified, mapped, characterized in terms of their neuroanatomical and biophysical features (Syková and Chvátal, 2020) and included in formal network models (Guidolin et al., 2007; 2017). The second concerns the level of highest miniaturization of the CNS network organization, where protein-protein allosteric interactions generate molecular networks performing integrative functions already at the plasma membrane level, suggesting they could be of relevance for connectomics (Sala et al., 2023). In this respect, of the greatest importance are direct (structural) receptor-receptor interactions, playing a role in setting synaptic efficacy and in memory processes (Agnati et al., 2003; Guidolin et al., 2007).

Finally, it must be observed that the connectome is a dynamical entity, undergoing changes during lifetime. A number of connectomics-based studies concerning typical and atypical development of human brain neuronal networks from birth to early adulthood are presently available (see Cao et al., 2016, for a review) and, as briefly discussed above, the number of studies on the modifications induced by the normal aging process is increasing (see Zuo et al., 2017). In this respect, however, a better understanding of the relationship between brain structure (at all the organizational levels) and behavior across the whole life span still represents a defining agenda for the next future. This effort, indeed, may help to better discriminate the effect that pathologic aging and disease processes have on the declining CNS architecture, as well as the interventions aimed at targeting these conditions.

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