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The brain as a "hyper-network": impact on neurophysiology and neuropharmacology

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Abstract. Neuronal network architecture plays a crucial role as the structural substrate for the brain functions. Increasing evidence, however, indicates that, beside neural networks, to fully understand brain complex integrative actions glial cells and the diffusion of signaling substances in the network of extracellular fluid channels should also be considered. To account for this more complex architecture it has been proposed that all these networks are assembled into a so-called brain hyper-network, having as fundamental components the multi-partite synapses involving not only neurons, but also regulated by the astrocyte networks and fine-tuned by microglia and by pervasive signals diffusing in the interstitial channels of the extracellular matrix. The main features of this view of the central nervous system organization are here discussed. This complex network architecture can be of particular interest for neurophysiology, since it may represent a suitable structural counterpart of physiological mechanisms allowing goal-directed behavior. Furthermore, a model of brain organization integrating the activity of different CNS components may assist in the identification of new possible targets for the pharmacological treatment of CNS diseases. These aspects are also briefly discussed.

Keywords: multi-partite synapse, intercellular communication, astrocyte networks, extracellular matrix, receptor complexes.

INTRODUCTION

In the last decades a large body of new evidence on central nervous system (CNS) structure and function has been acquired by morphological investigations based on a combination of different approaches, such as chemical neuroanatomy methods (histology, histochemistry, and immunocytochemistry), new techniques in microscopy (e.g. confocal or atomic force microscopy), and brain imaging technologies. A next key step was the possibility

of quantitative analysis of the obtained images, mainly achieved by the application of computer-assisted image analysis methods (Guidolin et al., 2022). This combination of different approaches led to a view of the CNS as a huge network of cells, regions, and systems in which intercellular communication processes virtually determine all aspects of the integrative function performed (see Agnati et al., 2023 for a discussion).

The network architecture plays a key role as a structural substrate for the CNS functions as indicated by the increasing interest for the connectomics, the comprehensive study of all aspects of neuronal connectivity (Lichtmann & Denk, 2011; Sporns, 2012). This field, representing a great scientific challenge in neuroanatomy, has developed very rapidly in the last years, allowing the characterization of the anatomic connections of large brain regions and functional neural subcircuits (Hagmann et al., 2007; Gong et al., 2009; Briggman et al., 2011; Van Essen et al., 2012; Wang & He, 2024; see also https://www.humanconnectome.org/).

In this respect, however, it is noted that although the fundamental anatomical substrate of CNS function are neural networks resulting from synaptic contacts among neurons, they do not deal exhaustively with the issue. About 40 years ago, several authors (see Hökfelt et al., 1986) demonstrated that one neuron could synthesize more than one neurotransmitter and a single postsynaptic site may express different types and subtypes of receptors for a given transmitter, with each receptor controlling a different decoding mechanism. Thus, a synapse becomes endowed with multiple communication/transmission lines. Furthermore, our group and other groups (see Guidolin et al., 2017 for a review) provided new data on the communication modes in the CNS that, while not dismissing the fundamental relevance of synaptic contacts, allowed to identify (Agnati et al., 1986) the existence of two main modes of intercellular communication in the CNS, generically called wiring transmission (WT: point-to-point communication as in the synaptic transmission) and volume transmission (VT: communication by diffusion in the extracellular/cerebrospinal fluid).

In the 1990s (see Araque et al., 2001), a broadened view on the cellular organization of the CNS was also provided with the demonstration that neurotransmitters can elevate astrocytic calcium levels as the result of the release of calcium from internal stores. This wave of intracellular calcium elevation was shown to propagate through gap junctions (Allen and Barres, 2005) between astrocytes for hundreds of micrometers (Cornell Bell et al., 1990), indicating the existence of astrocytic networks. In the involved astrocytes the calcium signal stimulates the release of gliotransmitters (such as D-serine, ATP, glutamate), leading to a direct regulation of ongoing synaptic activity (Fellin and Carmignoto, 2004). In this context, of particular interest have been ultrastructural investigations (Ventura and Harris, 1999) indicating that a high number of thin filopodia- and lamellipodia-like astrocytic processes (called PAP) can contact and enwrap synapses, the sites of neuronal communication, sometimes completely encapsulating them. Thus, the function and efficacy of synaptic transmission are determined not only by the composition and activity of pre- and postsynaptic components but also by the features of the PAP that enwrap the synapse. This evidence led to the proposal of the concept of "tripartite synapse" (Araque et al., 1999), providing a link between neural and astrocytic networks.

Although most of the available histochemical studies focused mainly on nerve cells, extracellular molecular networks have been revealed to play significant roles in the functional and structural organization of the brain (see Agnati et al.,2006 for a review). Extracellular matrix (ECM) components are synthesized by both neurons and astrocytes and are involved in the formation, maintenance, and function of synapses in the CNS (Dzyubenko et al. 2016; Rauch, 2004). Furthermore, they have a key role in the VT intercellular communication, since this communication mode is based on the diffusion of neuroactive substances in the brain extracellular space and their binding to extrasynaptic high-affinity receptors on neurons or glia (Nicholson and Sykova 1998; Agnati and Fuxe, 2000; Marcoli, 2015).

The possibility to integrate the abovementioned findings in a new overall view has been explored. In particular, the conceptual model of the brain as a hypernetwork (BHN, including neural networks, glial networks and ECM as components) has been proposed by our group (Agnati et al., 2006; 2018; 2023; Guidolin et al., 2017). It is schematically illustrated in Fig. 1 and its main features are discussed below. This complex network architecture can be of particular interest for neurophysiology, since it may represent a suitable structural counterpart of physiological mechanisms allowing goal-directed behavior, as those addressed in the framework of the theory of functional systems (see Sudakov, 1997). Furthermore, a model of brain organization integrating the activity of different CNS components may also assist in the identification of new possible targets for the pharmacological treatment of CNS diseases (Marcoli et al., 2023). A brief discussion of these aspects will be provided in the sections that follow.

THE BRAIN AS A HYPER-NETWORK

The architecture of the CNS extends 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. As far as the neuronal networks are concerned, evidence has been provided that the connections between different brain areas exhibit an organization called "small- world networks" (Watts and Strogatz, 1998; Liao et al., 2017), forming clusters of nearby areas with short links, which, in turn, have long-range connections to other clusters (Sporns and Zwi, 2004; Stam and Reijneveld, 2007).

Based on these observations, CNS tissue can be described as composed of a set of compartments or "functional modules" (FM; Agnati and Fuxe, 1984; Robertson, 2013) delimited by plastic boundaries. Thus, as illustrated in Fig. 1A, FM were considered the basic organizational level of the BHN architecture proposed for the CNS (Agnati et al., 2018). Typical examples of FM are provided by the human cerebral cortex, where 100 or more anatomical regions can be defined (Wig et al., 2011).

Available anatomical findings on these cortical areas also provide suggestions concerning the internal architecture of each FM. They, indeed, appear organized in cortical columns (Lorente de Nò, 1938; Mountcastle et al., 1957), cylinders composed of vertical chains of cells crossing all cortical layers. As stated by Rakic (Rakic, 2008), cortical columns can be considered functional units subserving a set of common static and dynamic cortical operations. A similar organization appears to characterize thalamus (Boeken et al., 2023), hippocampus (Caroni, 2015), basal ganglia (DeLong and Wichmann, 2009) and cerebellum (Leggio and Olivito, 2018). Within each cortical column (diameter in the range of 300–500 μm) minicolumns (diameter of about 50 μm) can be distinguished (Pethers and Sethares, 1996). According to Rinkus (Rinkus, 2010) they have a generic functionality, which only becomes clear when seen in the context of the function of the higher level, subsuming unit, the cortical column. Thus, a FM can be modeled (Agnati et al., 2018;2023) as formed by microcircuits (Fig. 1B) in which neurons and glial cells (mainly astrocytes) are organized into specific patterns to carry out processing activities (Shepherd, 2011).

Concerning the intercellular communication within FM and among FM, WT processes play a key role, being the involved neurons connected by means of synaptic contacts, and astrocytes through gap junctions (mediating the propagation of calcium signals between them). The intercellular communication between the cells in the CNS, however, is not limited to specific districts of these cells, such as synaptic regions or gap junctions (where the involved cells are in contiguity), but it also includes processes of VT, based on the release of signaling molecules and their diffusion in the extra-cellular space (see Guidolin et al., 2017 for a review) for a distance greater than the synaptic cleft. Typical chemical signals diffused by VT (see Guidolin et al., 2017; Agnati et al., 2023) include neurotransmitters, neuromodulators, growth factors, hormones, ions (e.g., Ca2+ ions) and gases (e.g., NO, CO_2, CO). This communication mode uses the several often spatially divergent tortuous channels made by the clefts (about 20 nm in diameter) between cells and filled with extracellular fluid and extracellular matrix (Chen and Nicholson, 2000). VT, therefore, is characterized by a very high divergence, since one source usually can send signals to a great many targets, including not only neurons and astrocytes but also other types of cells in the CNS, such as microglial cells (Färber and Kettenmann, 2005). In this respect, of potential interest is also the suggested possibility that electric fields produced by neuronal activity (Anastassiou and Koch, 2015) and magnetic fields associated with Ca^{2+} transients in astrocytes (Martinez-Banaclocha, 2017), if strong enough and/or positioned precisely, could influence the electrical excitability of neighboring neurons through a process called ephaptic coupling (Hales and Pockett 2014; Scholkmann 2015; Agnati et al., 2018). This multifaceted pattern of signaling leads to the formation of "complex cellular networks," exchanging signals in a certain volume of brain tissue and, due to this cross talk, integrating their activity (Agnati and Fuxe, 2000).

In this context, of particular interest is the role played by astrocytes at the level of the "tripartite" synapses (Araque et al., 1999), the structures providing a direct link between neural and astrocytic networks. As a response to synaptic activity (Heller and Rusakov 2015; Ghézali et al. 2016), indeed, astrocytes associated to these structures are able to rapidly (time scale of minutes) restructure their peri-synaptic processes modifying the coverage of the synaptic contacts (Reichenbach et al. 2010; Bernardinelli et al. 2014). Such a sophisticated control of the PAP's plasticity, therefore, could allow moving from a high privacy of the synaptic transmission (close enwrap of the synapse) to a more or less broad opening of the enwrapping. This would lead to diffusion by VT of signaling molecules also to neighboring astrocytes, neurons and other glial cells (Grillner and Graybel, 2006; Dallerac et al., 2013; Marcoli et al., 2015; Agnati et al., 2018; Semyanov, 2021). To account for this more complex network of signaling, more recently the concept of "multi-partite synapse", whose dynamics involves

not only neuronal synapses and astrocytes but also the extracellular matrix and microglial cells, has been proposed (Agnati et al., 2018; 2023; Aramideh et al., 2021). It is schematically illustrated in Fig. 1C.

It is well known that at the cellular level membrane receptors represent the key mechanism to decode the incoming signals. Experimental findings also showed that these elements of the cell decoding apparatus can be transferred to another cell via the exosome pathway (see Guidolin et al., 2023a for a review), enabling the target cell to transiently acquire the capability to decode signals for which it does not express the pertinent receptors. This process (called "roamer-type" of VT) represents a mechanism of plasticity for intercellular communication. In the 1980s, *in vitro* and *in vivo* experiments by Agnati, Fuxe and collaborators (Agnati et al., 1980; Fuxe et al., 1983) provided indirect evidence that a major class of cell receptors (the G protein-coupled receptors, GPCR), able to signal as monomers, can also establish structural receptor-receptor interactions (RRI), leading to the formation of receptor complexes (dimers or high order oligomers) at the cell membrane (see Fuxe et al., 2007 for historical details). In the years that followed, several groups (see Guidolin et al., 2022 for references) provided direct evidence for the existence of this molecular organization by exploiting a set of experimental techniques able to detect the spatial proximity of protein molecules (Trifilieff et al., 2011; Petazzi et al., 2020). The basic molecular mechanism characterizing the receptor assemblies are allosteric interactions (Changeux and Christopoulos, 2017), allowing the transfer of the energy associated with conformational or dynamic changes at some site of a protein to other sites, that will change their conformational or dynamical features accordingly. The resulting collective dynamics of these supramolecular structures allows the integration of different incoming signals reaching the plasma membrane to initiate specific patterns of signal transduction (Fuxe and Borroto-Escuela, 2016). Interestingly, bioinformatics approaches indicated that the dynamics of receptor complexes can be described by suitable networks models (Guidolin et al., 2007) suggesting that the connections between cells are themselves networks (molecular networks).

As illustrated in Fig. 1D, according to the above discussed features the BHN model appears to display a hierarchical or nested ("russian doll") architecture (Agnati et al., 2018; Guidolin et al., 2023b), providing a unified view of the different spatial scales (from the macro-scale of brain areas and FM, to the nano-scale of the molecular networks) characterizing the brain network organization. This view, supported by experimental findings focused on neuronal networks (see Sporns et al., 2005), can be discussed in the frame of Jacob's proposal (Jacob, 1977) on evolution working not as an engineer but as a tinkerer. Jacob claims that evolution tinkers together contraptions in a natural selection process that acts by adding direction to changes, orienting chance, and slowly and progressively producing more complex structures.

ANATOMICAL ARCHITECTURE AND NEUROPHYSIOLOGY

The search for understanding the role of CNS in the control of physiological functions has been classically subdivided into two disciplines, neuroanatomy and neurophysiology, which analyze from complementary perspectives the structural and functional properties of the CNS. As evidenced by the work of the neurobiological pioneer Santiago Ramon y Cajal (1852-1934), however, this historical dichotomy was never absolute (Borst and Leibold, 2023). He, indeed, always studied anatomic structures with reference to functional insights and modern functional imaging techniques (Friston, 2009) make the distinction quite blurred.

For centuries physiology based its view of the role of CNS function on the 'reflex principle' (see Sudakov, 1997 for a discussion), assigning a leading role to sensory stimuli, whose propagation along nerve fibers, from receptors to specific nerve centers, would allow the production of a reflected action as a final stage. According to this view, brain areas should be highly selective and exhibit considerable specialization, each responding to a set of inputs and contributing primarily to a single cognitive domain. Reflex theory, however, failed to provide a satisfactory explanation of many complex phenomena (Sudakov, 1997). This especially concerns goal-directed behavior. Reflex theory, indeed, had a difficulty in explaining why living organisms are so skilled in inventing means to correct their behavioral errors, and why their activity is not limited to responses to external stimuli but goes on until a certain vitally important result is achieved.

In the early 1940s an alternative view, called 'theory of functional systems' (TFS), was proposed (Anokhin, 1937). According to this view, some organism need is the dominant factor driving the organization of brain activities to achieve a result. This occurs through a flow of information (sensory, contextual, motivational, mnemonic) reaching brain areas, leading to their self-organization in order to define a goal and trigger possible goal-directed actions (Müller et al., 2021). When the goal is being set, however, we have the goal but not the result (Vityaev and Demin, 2018). Thus, the brain organization is pro-

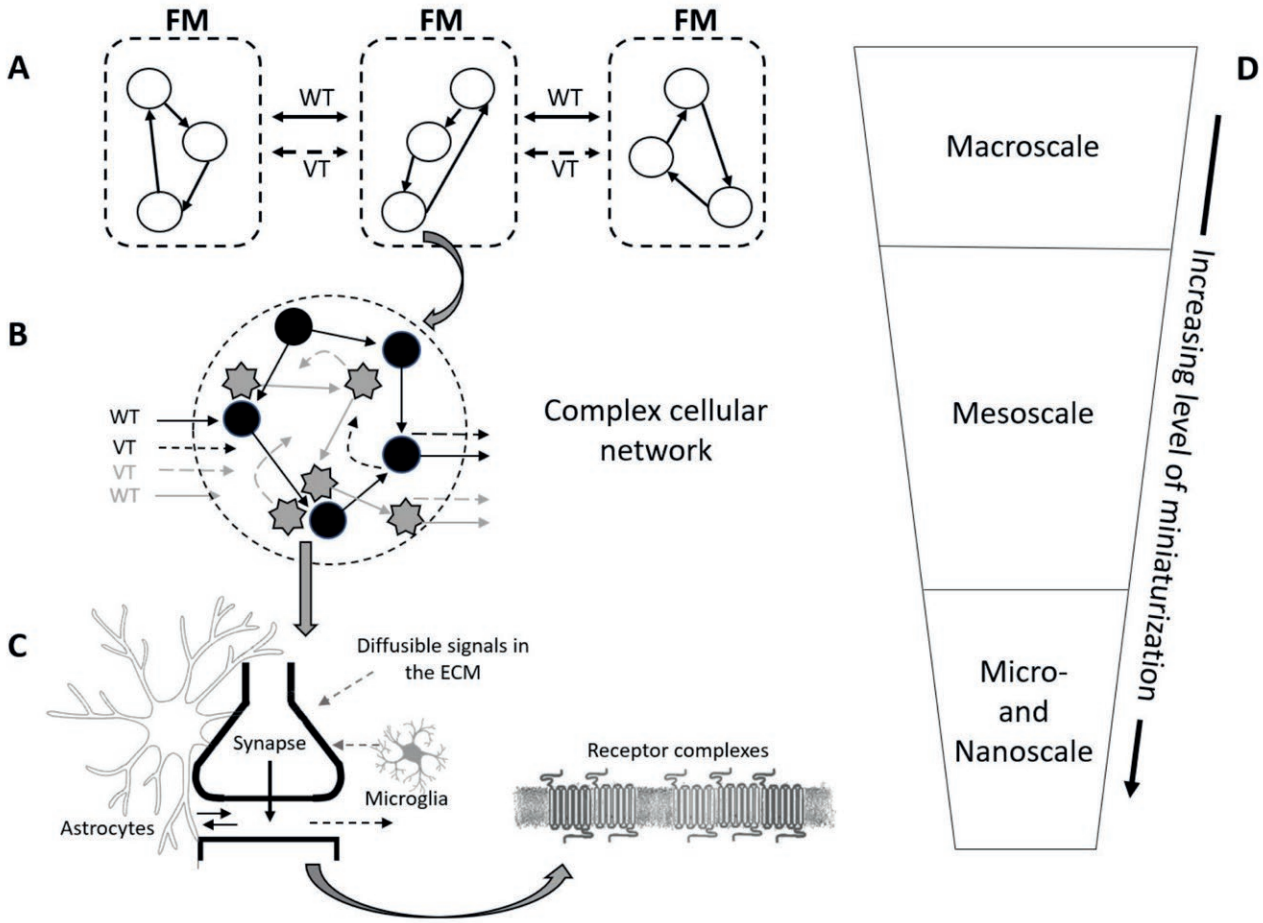

Fig. 1. Schematic illustration of the BHN view of the CNS organization. **A.** CNS tissue can be described as a network of FM linked by WT (solid arrows) and VT (dashed arrows) signaling pathways. **B.** Each FM can be modeled as formed by microcircuits involving neurons (in black) and glial cells (in grey) communicating by WT (neurons and astrocytes) and/or VT. **C.** Crucial components of this organization, are multi-partite synapses, whose dynamics involves not only neuronal synapses and astrocytes but also the extracellular matrix and microglial cells. Furthermore, at the cell membrane receptor proteins can form quaternary structures (receptor complexes). The collective dynamics of these supramolecular structures allows the integration of different incoming signals reaching the plasma membrane to initiate specific patterns of signal transduction. **D.** According to the BHN view the CNS tissue exhibit a hierarchical organization with networks of increasing miniaturization nested within each other.

gressively adjusted depending on mechanisms of feedback on the degree of usefulness or value of the currently obtained result (Anokhin, 1974; Vityaev and Demin, 2018). The brain functional organization, therefore, is not seen as a rigid design, but rather as a constantly changing dynamic structure. Only the elements that lead to the desired result are selected, and this selection is in a constant flux and evolution (Müller et al., 2021).

In this respect, being composed of a network of FM, the BHN model of brain architecture fits with this physiological view of CNS function and provides support to that view. The model, indeed, is consistent with findings from brain imaging studies showing that most regions of the brain appear to be activated by multiple tasks across diverse task categories (Anderson et al., 2010). As an example, studies on the Broca's area (see Poldrack, 2006), showed that the current notion of the Broca's area as a specific "language" region is weak, since it was more frequently activated by non-language tasks than by language-related ones. These findings suggest that the brain achieves its variety of functions by putting the same regions together in different patterns of functional cooperation.

The possibility of different patterns of activity is a typical feature of the dynamics of systems characterized by a network architecture. In other words, when started from an initial configuration generated by external inputs, a network system can rapidly converge to one of a number of temporary equilibrium configurations

or 'attractors' (Wuensche and Lesser, 1992; Guidolin et al., 2007; Pereira and Brunel, 2022; Ashwin et al., 2024). Thus, the BHN model of CNS architecture may also represent a suitable structural counterpart of this physiological process.

In this respect, a further intriguing aspect emerges when the hierarchical architecture of CNS suggested by the BHN view is considered. Physiological processes, indeed, are in general controlled at multiple cellular levels and neural circuits indicating a hierarchical functional organization (Nederbragt, 1997) allowing an increasing level of integration of the incoming information. Reported examples include the maintenance of homeostasis (Stevenson, 2024) and visual perception (Gilbert, 2013; Gämänut and Shimaoka, 2021; Lima et al., 2023).

A last point, however, has to be emphasized. As mentioned before, a complex flow of information is physiologically important to trigger possible goal-directed actions. In this respect, the hypernetwork architecture can be of specific interest. This architecture, indeed, considers a spectrum of signals reaching brain areas not limited to neuronal synaptic signaling, but also involving signals between astrocytes, between neurons and glial cells, as well as signals (such as growth factors, hormones, ions, and gases) reaching the nerve cells by VT pathways. Therefore, the use by brain areas of contextual information to define their functional organization is intrinsically present in the BHN view of CNS architecture.

ANATOMICAL ARCHITECTURE AND NEUROPHARMACOLOGY

A critical aspect of drug development in the therapy of neuropsychiatric disorders is the so-called "target problem" (TP), namely the selection of a proper target not simply based on the etiopathological classification of symptoms but rather on the detection of the supposed structural and/or functional brain alterations (see Marcoli et al., 2023 for a recent review).

In neuropharmacology the classical view of neuronal synapse is still the most followed reference framework on which drug discovery and development are based. Early findings, indeed, suggested that by acting at the synaptic receptor level, marked changes in integrative brain functions could be achieved (Kebabian and Greengard, 1971; Snyder, 2011; Giessing and Thiel, 2012). However, frequent failure of drugs in drug development and/or drug side effects, especially during chronic treatments, indicated that the TP was not well resolved by this direct approach (see, for instance, (Lipton, 2005) for N-methyl-D-aspartate receptor as drug target). A step forward was the characterization at synaptic level of iso-receptors (i.e. of receptor subtypes for the same neurotransmitter), offering the possibility of acting on recognition/decoding components of synaptic transmission capable of triggering some peculiar responses at synaptic level (see Snyder, 1984). Again, however, TP was not fully solved with the more selective drugs targeting isoreceptors. Indeed, although less severe than previously observed, side effects and/or treatment failures have been reported (Miller, 2010; Carhart-Harris and Nutt, 2017; Charvin et al., 2018).

The more comprehensive view of synapses as multipartite structures, as suggested by the BHN model of CNS organization (Agnati et al., 2023), may significantly expand the range of possibilities to addressing the TP (Marcoli et al., 2023). They, indeed, don't involve only neurons, but are also regulated by the astrocyte networks and fine-tuned by microglia (Miyamoto et al., 2013; Crapser et al., 2021) and by pervasive signals diffusing in the interstitial channels of the extracellular matrix.

In this context, membrane receptor complexes in neurons and glial cells have been proposed as key integrators, capable of converting multiple extracellular signals into appropriate cellular biochemical responses (see (Guidolin et al., 2021;2022;2024) for reviews). RRI, therefore, may provide new opportunities to optimize existing pharmacological treatments or to develop completely new pharmacological strategies. In this respect, the search for receptor heteromers' selective compounds would be of key importance to fully exploit their properties. At least three approaches could be followed to achieve this goal. The first, and presently most studied (see Guidolin et al., 2020), is based on the fact that, due to a different pattern of allosteric RRI, the conformational state of a given protomer may change according to the type of complex in which it is involved (Fuxe et al., 2013). Thus, the pharmacology of some agonists/antagonists of a given protomer in terms of affinity and efficacy may show substantial differences among various types of receptor complexes. A second approach to identify receptor complex selective compounds is based on the possibility that, when the complex forms, the quaternary structure could display novel specific allosteric sites suitable for the binding of some modulators (Cervetto et al., 2008). The use of bivalent ligands constitutes a third possible approach for targeting receptor heteromers (see (Hiller et al., 2013) for a review). A bivalent ligand consists of two pharmacophoric entities linked by an appropriate spacer. In this way, it should be possible to target GPCR heteromers by adequate, potent, and receptor complex-selective ligands. (see (Daniels et al., 2005) for examples). These research efforts are still in their

experimental phase. Some significant results, however, have been obtained, as exemplified by the adenosine A_{2A} receptor antagonist istradefylline (targeting the heterodimer between the A_{2A} receptor and the dopamine D_2 receptor), recently approved in the United States as an adjunctive treatment in Parkinson's disease (Chen and Cunha, 2020).

CONCLUDING REMARKS

As indicated by the rapid increase of studies addressing connectomics, the anatomical mapping of the relationship among CNS components can represent a significant advance to reach a deeper level of understanding of CNS functions. In fact, the integrative actions of networks in which functions emerge from sets of elementary units (nodes), linked by connections and bound together dynamically (Bullmore and Sporns, 2012), are probably the process allowing the brain to accomplish its activity. As pointed out by Sporns (Sporns, 2013), the emphasis on structure is important because anatomically determined connections among CNS elements embody a large but finite set of relations that (at least in principle) can be objectively characterized in terms of their geometrical and biophysical features.

To date, the characterization of the connectivity between neurons at a macroscale level (Gong et al., 2009) has been the major focus of the research effort in connectomics, allowing the demonstration of several topological features of the adult human neuronal networks (see Stam, 2010). Experimental and theoretical limitations of the present approach, however, exist and should be carefully considered. The major limitation rely to the assumption that all functionality of CNS could be derived once the complete pattern of connections between neurons has been recorded (see Sporns, 2013, for a critical analysis).

In this respect a particular aspect deserves consideration. It refers to the increasing evidence indicating that synaptic transmission is significantly complemented by other cell types (Araque et al., 1999; Miyamoto et al., 2013) communicating via two modes of connection, WT and VT (which are not mutually exclusive), and by a pattern of diffusing signals reaching the cells through the extracellular space (Agnati and Fuxe, 2000; Marcoli et al., 2015). The view of the CNS organization as a hyper-network tries to account for this more complex architecture to reach a deeper insight into the relationship between brain structure and function with potentially relevant implications of this enlarged view on neurophysiology and neuropathology (see Guidolin et al., 2017).

Obviously, at present, it is impossible to give detailed representations of the BHN. The possibility however exists to identify the brain areas where are mainly concentrated the supposed crucial components of this organization, namely the multi-partite synapses (where the dynamic reassembling of the different brain networks information handling processes appears to occur) and to consider these areas as nodes for an analysis of the BHN (see Robertson, 2013). A research effort in this direction could also complement imaging connectomics and provide a more complete drawing of the connectome plasticity in different functional conditions. Furthermore, it can be suggested that investigations on the functional plasticity of multi-partite synapses can be the background for a new understanding and perhaps a new modelling of brain integrative actions.

In the last 20 years, a significant research interest has also been focused on the nano-scale level of the BHN, namely on molecular networks at the cell membrane of neurons and glial cells (see Guidolin et al., 2021), and in particular on receptor complexes. They, indeed, may provide new opportunities to optimize existing pharmacological treatments or to develop completely new pharmacological strategies. In this context, a topic of possible development would also be the identification of pharmacological tools separately targeting synaptic and extrasynaptic receptors (Hoestgaard-Jensen et al., 2013) in order to design strategies to rebalance WT and VT. In the neuropharmacological field, finally, an important direction of future research is certainly targeting glial cells as a strategy to treat neurological disorders (Cervetto et al., 2023). As suggested by the BHN view, indeed, the intimate association of glia with neurons is at the basis of increasing evidence that metabolic perturbations of glial cells may alter neuron–glial interactions, potentiating the underlying pathology of many neurological diseases (Afridi et al., 2020). The mechanism driving the circumstantial activation of glial phenotypes, however, is just starting to unravel, and future studies should open new perspectives.

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