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The Relevance of a Philosophical Toolkit to Advance Neuroscience

The Role of Complexity Theory in Understanding Brain's Neuron–Glia Interactions

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ABSTRACT

Brain information processing complexity is conventionally recognized as derived from neuronal activity, with neurons and their dynamic signalling responsible for the transfer and processing of information. However, the brain also contains other non-neuronal cells, glial cells, which exceed the number of neurons and are involved in the processes related with information coding by neural networks and underlying brain functions. Decisive advances in the characterization of the molecular and physiological properties of glial cells shed light on their active roles in neurotransmission and neuronal physiopathology. This expanded relationship between neurons and glia challenges traditional neurobiology by highlighting their reciprocal influence, where it is difficult to determine whether neuronal or glial processes initiate and drive the interactions. This interplay creates a dilemma, where the causal hierarchy between these two cell types remains unresolved. A philosophical tool, the 'Theory of Complexity' of Edgard Morin can help to better explain and study the complexity of neuron–glia interactions. Morin's proposal on complexity is useful to transform brain knowledge, in order to review the brain molecular functions in antireductionist pattern. In this manuscript, we will discuss how to use the 'retroactive loop' principle from Morin's 'Theory of Complexity' at the brain molecular level, proposing a new philosophical-experimental grid that can help neuroscientists for a better understanding of the glia–neuron interactions in the brain.

1 | Introduction

1.1 | The Glial Cells in the Brain

Brain information processing is conventionally recognized as derived from neuronal activity, with neurons and their dynamic signalling responsible for the transfer and processing of information (Majewska, Newton, and Sur 2006).

From the original descriptions of the cellular basis of the nervous system, neurons were promptly recognized as the main cellular elements involved in the transfer and processing of information, perhaps because they show cellular processes that extend towards sensory organs, muscles and glands. In addition, because electricity was known to be fundamental in nervous system function, the fact that neurons were electrically excitable further supported this idea. Indeed, it is well established that

Abbreviations: ATP, adenosine triphosphate; BBB, blood-brain barrier; CNS, central nervous system; 'Co', coevolution; GABA, gamma-aminobutyric acid; LPS, lipopolysaccharide; mEPSC, miniature excitatory postsynaptic current; 'RE', recursiveness; 'RE-CO grid', recursiveness-coevolution grid; TLR4, tool-like receptor-4.

neuronal electrical excitability is based on the expression of numerous ligand and voltage-gated membrane channels that give rise to membrane currents and membrane potential variations (Hille 2001; Araque and Navarrete 2010).

The brain also contains other non-neuronal cells, glial cells, whose exact proportion relative to neurons is still debated but appears to be comparable (Verkhratsky and Nedergaard 2018). These cells have been largely overlooked in relation to processes involved in information coding and handling by neural networks that underlie brain function. However, over the past 15 years, glial cells have become the focus of an increasing number of studies because of their significant involvement in various physiological and pathophysiological processes.

Decisive advances in the characterization of the molecular and physiological properties of glial cells have revealed that they may play active roles in neurotransmission and neuronal physiology (A. Araque, Carmignoto, and Haydon 2001; Perea and Araque 2007).

Three different types of glial cells are distinguished in the central nervous system (CNS; astrocytes, oligodendrocytes and microglia), each possessing distinct functions.

Astrocytes represent the most abundant fraction of glial cell types in the adult brain (Kettenmann and Ransom 2004). Among all glial cell types, several of the functional roles of astrocytes in the healthy adult brain are already well described. These functions are broad, spanning many aspects of brain physiology. They contribute to the brain's water and ion homeostasis, glucose and lipids metabolism. They also participate in the tripartite synapse as well as in the contribution to the blood-brain barrier (BBB) maintenance , where they can regulate the blood flow, nutrients and oxygen intake to the brain (Kimelberg 2010; Kimelberg and Nedergaard 2010; MacVicar and Newman 2015).

Microglia are the immunocompetent and phagocytic cells of the nervous system. Although they are a part of the brain's glia, unlike other glial cells, they do not originate from ectodermal tissue but from yolk-sac progenitors that colonize the brain only during development (Kim and de Vellis 2005; Kettenmann et al. 2011). Microglia have been shown to cover a vast volume of the adult brain parenchyma, with individual, non-overlapping domains that constantly monitor their environment through the rapid movements of their fine filopodia, responding to any type of insult (Nimmerjahn, Kirchhoff, and Helmchen 2005; Cronk and Kipnis 2013).

Oligodendrocytes are the myelinating cells of the CNS. They represent the final stage of a cell lineage that must go through a complex and precisely timed program of proliferation, migration and differentiation to ultimately produce the insulating sheath of axons, known as myelin (Bradl and Lassmann 2010).

All these glial cells are implicated in the brain functions and in neurological pathologies with the consequent impairment of proper neuronal function (Allen and Lyons 2018). Since the cell types in the CNS depend on their close connection and communication, the function of one cell type ultimately may lead to a specific effect on all other cells in the same environment or circuit. Thus, it is often impossible to discriminate cause and consequence in this complex cascade in the brain (Gupta et al. 2020).

2 | The Complexity of Neuron–Glia Interactions in the Brain at the Synaptic Level

The synapse is a fundamental element of the brain's complex network of neural connections. It serves as the critical junction where signals are exchanged between neurons, facilitating the communication necessary for cognitive functions, sensory perception and motor coordination (Barri et al. 2022). A deep understanding of synaptic structure and function is essential to unravel how the brain processes and stores information.

On a microscopic level, synapses are composed of presynaptic terminals, synaptic clefts and postsynaptic membranes (Cohen, Gianaros, and Manuck 2016). Neurotransmitters released from the presynaptic terminal cross the synaptic cleft and bind to receptors on the postsynaptic membrane, initiating electrical impulses, known as action potentials (Cohen, Gianaros, and Manuck 2016). This process of synaptic transmission enables neurons to relay information across neural circuits, forming the foundation of neural computation and information processing.

2.1 | The Tripartite Synapse

Astrocytes, through their intimate connections with synapses, play an active role in monitoring and modifying synaptic function, thereby regulating synaptic transmission in the brain (A. Araque, Carmignoto, and Haydon 2001). Over the past three decades, significant research has highlighted the crucial role of astrocytes not only in adult synaptic function but also in the development of synaptic connectivity during brain maturation (Chung, Allen, and Eroglu 2015).

The close structural and functional relationship between perisynaptic astrocytic processes and neuronal presynaptic and postsynaptic structures gave rise to the concept of the 'tripartite synapse' (A. Araque, Carmignoto, and Haydon 2001). Astrocytes influence synaptic function by regulating presynaptic activity and postsynaptic receptor dynamics, utilizing a variety of signals to fine-tune synaptic strength (Chung, Allen, and Eroglu 2015).

Presynaptic connection strength is influenced by factors such as release probability—the likelihood that neurotransmitter vesicles being released from the presynaptic terminal in response to an action potential—and quantal content, which reflects the number of vesicles released per action potential (Chung, Allen, and Eroglu 2015; Newman et al. 2022). The number of functional neurotransmitter receptors clustered at the postsynaptic density determines postsynaptic strength (Chung, Allen, and Eroglu 2015; Newman et al. 2022). The response size can vary depending on receptor density, receptor subunit composition, phosphorylation status and receptor stability within the postsynaptic density. Analysis of individual synaptic events, such as miniature excitatory postsynaptic currents (mEPSCs), is commonly used to assess postsynaptic strength, as mEPSCs reflect the response of a single synapse to the release of a single vesicle

containing neurotransmitter, providing insight into the strength of the postsynaptic response (Ohan and Johnston 2005).

Further studies using more intact preparations, such as brain slices, have shown that astrocytes sense synaptic activity through the expression of ion channels, transporters and receptors (A. Araque, Carmignoto, and Haydon 2001; Alfonso Araque et al. 2014; Volterra, Liaudet, and Savtchouk 2014). The astrocyte calcium signal can be triggered by various synaptically released neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), acetylcholine, endocannabinoids, adenosine triphosphate (ATP), norepinephrine and dopamine (Alfonso Araque et al. 2014; Haydon and Carmignoto 2006; Perea, Navarrete, and Araque 2009).

Astrocytes can, in turn, release neuroactive molecules, known as gliotransmitters, such as glutamate, GABA, ATP, adenosine or D-serine, which activate neuronal receptors (Alfonso Araque et al. 2014; Halassa and Haydon 2010; Volterra and Meldolesi 2005). Multiple mechanisms have been proposed to mediate gliotransmitter release, with the calcium-dependent pathway being particularly notable due to its link with astrocyte excitability (Verkhratsky and Nedergaard 2018). Through the release of gliotransmitters, astrocytes modulate neuronal activity and synaptic transmission across various brain regions, impacting both neural circuit function and behaviour (Figure 1; Alfonso Araque et al. 2014; Perea, Navarrete, and Araque 2009; Kofuji and Araque 2021; de Oliveira et al. 2015).

The functional implications of this astrocytic regulation are profound. A single astrocyte may interact with over 100,000 synapses (Bushong et al. 2002), each of which can be independently regulated (A. Covelo and Araque 2016). Moreover, individual astrocytes can release different gliotransmitters with specific regulatory effects at different synapses (Ana Covelo and Araque 2018). This complexity is further amplified when considering that brain regions contain thousands of astrocytes, each regulating thousands of synapses within local circuits. Collectively, the regulatory role of astrocytes at individual synapses adds a significant degree of complexity to the potential functional states of synapses, thereby greatly enhancing the computational power of neural circuits.

2.2 | Microglial Cell at the Multipartite Synapse

The tripartite synapse model has been expanded to the concept of the multipartite synapse, incorporating interactions with

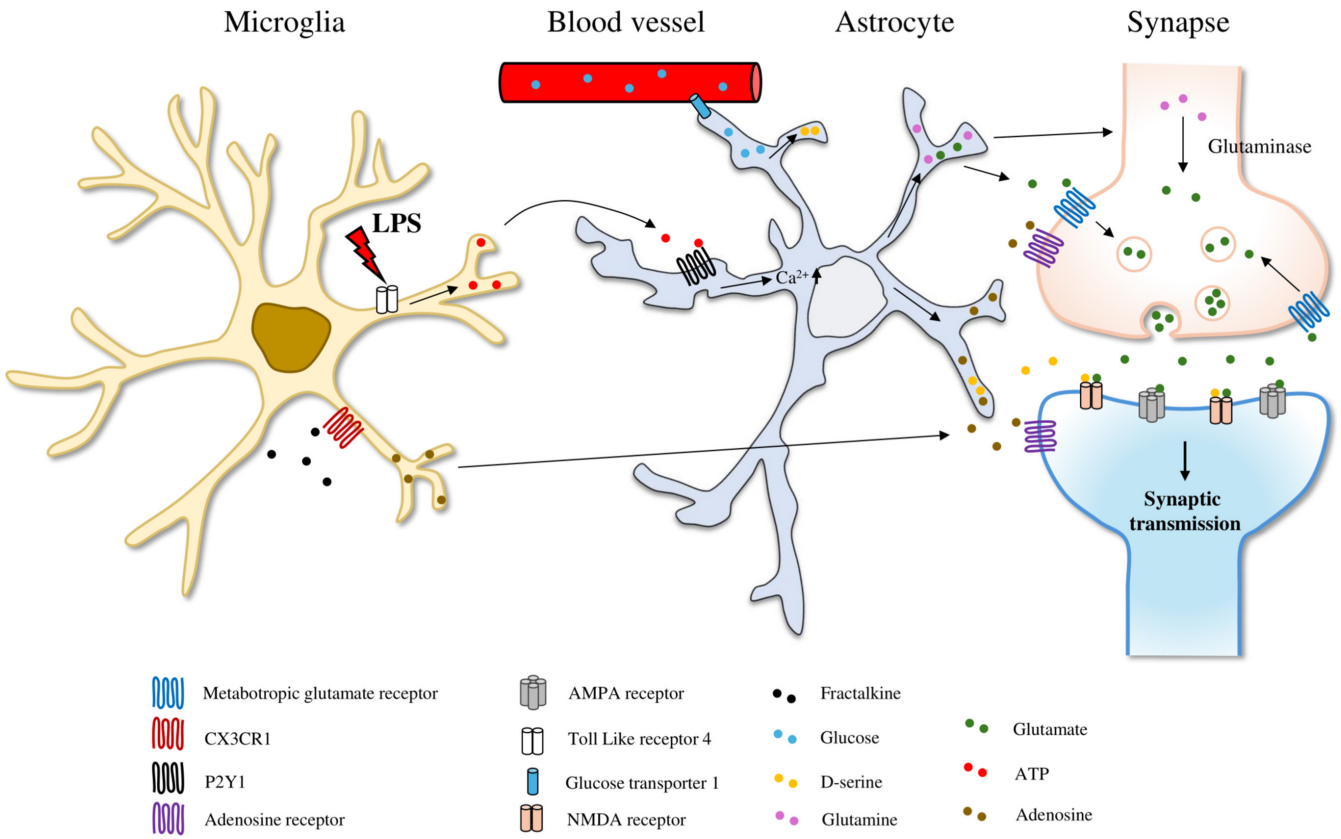

FIGURE 1 | Simplified schema of glia–neuron interactions regulating synaptic transmission. Lipopolysaccharide (LPS) or endogenous ligands bind to the TLR4 receptor on microglia, triggering a signalling cascade that leads to ATP (red dots) secretion. This ATP activates the P2Y1 receptor on astrocytes, inducing intracellular calcium oscillations. Consequently, astrocytes increase the production and release of D-serine (yellow dots), adenosine (brown dots) and glutamine (pink dots)/glutamate (green dots). Astrocytes uptake glucose (blue dots) from the bloodstream via Glucose Transporter 1 (GLUT1), metabolizing it either for energy production or for D-serine synthesis. D-serine, once secreted, coactivates NMDA receptors alongside glutamate. Additionally, astrocytes release glutamine, which neurons convert into glutamate, or they can directly secrete glutamate for neuronal uptake and synaptic transmission. Adenosine, also secreted by microglia upon Fractalkine (black dots) binding to its CX3CR1 receptor, is detected by astrocytic adenosine receptors, further modulating neurotransmitter release.

neighbouring microglia that periodically contact the synaptic structures (Nedergaard and Verkhratsky 2012; Verkhratsky and Nedergaard 2014). Under physiological conditions, microglia respond quickly to neuronal activity by modulating their numerous processes that continuously engage with synaptic elements (Wake et al. 2009; Tremblay et al. 2010). Thus, microglia may serve as precise sensors of neuronal activity, suggesting a potential for reciprocal control of neurotransmission. Microglia can rapidly modulate neuronal activity by the application of lipopolysaccharide (LPS; Pascual et al. 2012). LPS, a ligand that mimics bacterial infection, unveils pathological pathways and is recognized by tool-like receptor-4 (TLR4), expressed by microglia. This receptor can also be activated by several endogenous ligands as extracellular matrix components such as fibronectin, heparan sulphate or biglycan (Habich et al. 2005; Gondokaryono et al. 2007; Midwood et al. 2009; Milanski et al. 2009; Yu, Wang, and Chen 2010). Consequently, the mechanisms uncovered by LPS likely have physiological relevance. For example, LPS application to acute hippocampal slices induces a rapid, transient increase in the frequency of spontaneous synaptic AMPAergic currents in CA1 hippocampal neurons (Figure 1; Pascual et al. 2012).

Endogenous signals can also influence microglial activity significantly. For instance, damage-associated molecular patterns (DAMPs), which are released in response to cellular damage, interact with microglial receptors such as toll-like receptors (TLRs), initiating local inflammatory responses (Thundyil and Lim 2015). Similarly, stress—whether chronic, physical or psychological—can affect microglial function. Microglial overactivation by social defeat stress has been shown to contribute to anxiety- and depressive-like behaviours (Nieto-Quero et al. 2021). Furthermore, stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis modulates microglial activity, influencing neuroinflammation and synaptic plasticity (Sugama and Kakinuma 2020; Hassamal 2023). Chronic stress has also been linked to low-grade brain inflammation and microglia activation, both of which play a role in psychiatric disorders such as depression and anxiety (Ferat-Osorio, Maldonado-García, and Pavón 2024).

Microglia do not solely respond to damage but are also actively involved in maintaining neuronal activity and regulating synaptic plasticity under physiological conditions. However, hyperactivation due to harmful stimuli can lead to chronic neuroinflammation, impairing neuronal functions and contributing to various neurological and psychiatric disorders (Cornell et al. 2022).

Experimental studies have provided further insights into the dialogue between microglia and neurons. For example, the deletion of specific microglial genes and RNA sequencing techniques have revealed key microglial roles in neuronal regulation. Knockout studies of fractalkine and P2Y12 receptors have shown reduced microglia–neuron interactions and increased seizure severity, highlighting the importance of these receptors in microglial activity (Eyo et al. 2014; Badimon et al. 2020). Moreover, microglial responses to neuronal activation include distinct transcriptional changes. Controlled neuronal activation, followed by microglia-specific RNA sequencing, has revealed upregulation of genes associated with chemotaxis and actin filament polymerization, indicative of enhanced microglial migration and structural adaptation (Badimon et al. 2020). These findings underscore the dynamic and reciprocal interactions between microglia and neurons, with significant implications for CNS health and disease.

Among their multifaceted functions, microglia release extracellular vesicles (EVs), including microvesicles, as critical mediators in the context of multipartite synapses. In this dynamic environment, microglial EVs serve as messengers that regulate synaptic plasticity and modulate responses to environmental changes (Cabrera-Pastor 2024). These microvesicles, ranging in size and molecular composition, carry a variety of bioactive molecules such as proteins, lipids and nucleic acids, which can influence neuronal and glial functions (Ceccarelli et al. 2021).

Moreover, EVs from microglia can carry pro-inflammatory cytokines or complement components, contributing to synaptic pruning under both physiological and pathological conditions (Gabrielli et al. 2022). These vesicles participate in intercellular signalling, mediating crosstalk between neurons, astrocytes and other glial cells, thereby reinforcing the integrative nature of multipartite synapses (Porro, Trotta, and Panaro 2015).

One specific mechanism by which microglia influence synaptic functions involves the release of microvesicles a few seconds after ATP stimulation, likely through a P2X7-dependent pathway (Bianco et al. 2005). When these vesicles were extracted from cultured microglia and applied to cultured hippocampal neurons, they increased the frequency of mEPSCs, presumably through presynaptic regulation (Antonucci et al. 2012). Moreover, analysis of the signalling pathway between microglia and synapses indicates that microglial microvesicles modulate mEPSCs via a phosphatidylinositol-dependent mechanism that regulates presynaptic vesicle release (Antonucci et al. 2012).

Recent studies have also highlighted the role of microglial EVs in neuroinflammatory and neurodegenerative diseases, where their molecular cargo is altered, potentially amplifying pathological processes. For instance, EVs enriched with complement proteins have been implicated in abnormal synapse elimination, a phenomenon linked to neurological disorders such as Alzheimer's disease (Gu et al. 2023). These findings emphasize the dual role of microglial EVs as both biomarkers and active participants in the modulation of synaptic networks.

Understanding the release and function of microglial EVs within multipartite synapses provides valuable insights into the complexity of neuron–glia interactions and opens new avenues for therapeutic interventions targeting EV pathways in CNS disorders.

Although the functional relevance and specificity of this mechanism are yet to be fully established, these studies propose the intriguing hypothesis that physical interactions or membrane exchanges between microglia and neurons could actively and swiftly regulate neurotransmission.

2.3 | Omics Techniques to Implement the Study of Neuron–Glia Interactions

The advent of 'omics' techniques, encompassing methods for the comprehensive analysis of macromolecules at various scales, have revolutionized our understanding of neuron–glia interactions. For example, transcriptomics enables the examination of the full set of RNA molecules expressed by a cell, anatomical region, or individual, paving the way for discovering novel molecular targets under controlled conditions (Zhang et al. 2014). Through omics approaches such as genomics, transcriptomics, proteomics and metabolomics, researchers can systematically explore how neurons and glial cells interact and adapt to environmental stimuli, developmental processes and pathological states (Barres 2008).

Genomics and transcriptomics focus on analysing gene expression and its alterations in response to specific stimuli, revealing the transcripts (RNAs) produced by distinct brain cell types. These techniques are instrumental in delineating the molecular signatures of neuronal and glial responses. In contrast, proteomics and metabolomics provide a deeper understanding of protein interactions and metabolic adaptations triggered by external factors, such as stress and environmental changes. Together, these methodologies facilitate an integrated exploration of how neurons and glia communicate, shedding light on their contributions to brain functions (Barres 2008).

Dynamic investigations by omics techniques offer valuable insights into the intricate chemical signalling networks between neurons and glial cells. For instance, such approaches enable the mapping of molecular dialogues, enhancing our comprehension of how cell-to-cell interactions contribute to complex brain functions like learning and memory. One notable application of transcriptomics is illustrated by studies in mouse models of Alzheimer's disease, where a strong interconnection between dysregulated genes in microglia and astrocytes has been identified. This evidence highlights a continuous and coordinated dialogue between these cell types in response to pathology. Specifically, research has shown that increased expression of the complement molecule C1q by microglia induces elevated expression of C4 by astrocytes, which may contribute to enhanced synaptic elimination (Chen et al. 2020).

These findings exemplify how omics techniques can unravel the molecular underpinnings of neuron–glia communication, revealing shared cellular responses and their roles in the brain's adaptive and maladaptive processes. Such comprehensive approaches promise to bridge the gaps in understanding how cellular networks orchestrate brain functions in health and disease.

2.4 | Multimodel and In Vivo Experiments to Dissect the Complex Neuron–Glia Interactions

Recent advances in imaging technologies and recording methodologies have enabled researchers to visualize dynamic brain functions in vivo, providing unprecedented insights into neuron–glia interactions. These techniques, often applied in animal models, have proven invaluable for investigating the intricate crosstalk between neurons and glial cells. For instance, in vivo calcium imaging allows the monitoring of glial cell activity during different physiological and pathological states (Jager et al. 2024).

Different models and methodologies are being employed to address the complexity of neuron–glia interactions. In animal models, tools such as silicon probes have been utilized to record neural activity across multiple brain regions in freely behaving mice, offering a deeper understanding of how these interactions manifest during natural behaviours (Ferreira-Fernandes et al. 2023). Similarly, in vivo studies using neuroprobes have provided insights into the electrophysiological and astrocytic responses to neural implantation, shedding light on glial cell dynamics and their role in maintaining homeostasis in the brain (Mols et al. 2017).

Human studies have also contributed significantly to the field. For example, astrocyte uncoupling has been implicated in temporal lobe epilepsy, as observed in surgical resections from patients. These findings underline the critical role of astrocytes in regulating neuronal excitability and synaptic function (Bedner et al. 2015). In the context of glioblastoma, tumour-associated astrocytes have been shown to contribute to an immunosuppressive environment, emphasizing the importance of glial cells in pathological conditions and their potential as therapeutic targets (Henrik Heiland et al. 2019).

The integration of data from human and animal studies, coupled with methodologies such as calcium imaging, silicon probes and electrophysiological recordings, offers a more comprehensive understanding of neuron–glia interactions. By leveraging these complementary approaches, researchers can uncover the mechanisms underlying normal brain function and the dysregulation seen in neurological and psychiatric disorders.

Although experimental models, including in vivo and in vitro systems, provide invaluable insights into neuron–glia interactions, scientists must carefully consider species-specific differences when selecting models and interpreting results. These differences present significant challenges in translating findings to human physiology and pathology. Despite advances in the development of human brain models, such as organoids and ex vivo systems, these approaches still face limitations, including their inability to fully replicate the complexity of the human brain's cellular diversity, connectivity and dynamic microenvironment (Kelava and Lancaster 2016). Furthermore, ethical constraints and the technical challenges of accessing live human brain tissue further restrict the scope of human-centric studies (Dauth et al. 2017).

Nonetheless, the use of available human pathological tissue resections, such as those obtained from patients with epilepsy or brain tumours, has emerged as a valuable resource for translational research. These efforts have significantly advanced our understanding of brain pathologies and provided important insights into neuron–glia interactions within the human context (Milior et al. 2023). To capture the full complexity of neuron–glia interactions across species, a combined approach utilizing both animal models and human samples may offer a practical solution, bridging the gap between fundamental research and clinical applications.

3 | The Reductionist and Antireductionist Approaches to Describe Neuron–Glia Interactions in the Multipartite Synapse

The above-described studies suggest, but do not completely demonstrate, that astrocytes and microglia modulate synaptic function in the multipartite synapse, affecting the neuronal activities and consequently the brain functions. This interplay creates a dilemma, where the causal hierarchy between these two cell types remains unresolved. Does the neuronal activity determine the specific glia responses, or are the glial cells affecting first the neuronal activities at the synaptic level?

In neuroscience, the reductionist approach seeks to understand complex biological systems by dissecting them into simpler, more manageable components (Parker 2022). Applied to the study of neuron–glia interactions, this approach involves breaking down the intricate relationships between neurons and glial cells into discrete molecular and cellular mechanisms. By focusing on individual components such as neurotransmitters, receptors and signalling pathways, researchers aim to elucidate how these elements contribute to the dynamic communication between neurons and glia within the multipartite synapse.

Reductionism in neuroscience allows for a detailed examination of specific aspects of neuron–glia interactions, providing insights into fundamental processes such as synaptic transmission, neuroinflammation and synaptic plasticity. By isolating and manipulating key components experimentally, scientists can uncover underlying principles that govern the intricate interplay between neurons and glia in both health and disease states.

However, although the reductionist approach offers valuable insights into molecular mechanisms and cellular interactions, it is essential to acknowledge its limitations in capturing the holistic complexity of the brain. The challenge lies in integrating findings from reductionist studies into a comprehensive understanding of how neuron–glia interactions contribute to higher order brain functions and behaviours. Unlike the reductionist approach, which breaks down the complex system into simpler parts to understand its functioning, 'antireductionism' suggests that the emergent properties and functions of the nervous system cannot be fully explained by the sum of its parts. Antireductionism, in the context of neuron–glia interactions, emphasizes the importance of considering the nervous system as a whole, without reducing it to isolated molecular components or processes.

4 | The Theory of Complexity for an Antireductionist Approach in Neuroscience

The rise of the 'science of complexity' in the 1980s marked a major transformation in scientific and epistemological thinking. This innovative perspective, shaped by influences such as cybernetics, chaos theory and evolutionary biology, emphasizes the study of systems as interconnected, adaptive and emergent phenomena (Gare 2013). Thinkers like Edgar Morin, Ilya Prigogine and Gregory Bateson have played key roles in shaping this discussion, advocating for a holistic systemic approach that acknowledges the interdependence between parts and the whole (Prigogine, Stengers, and Prigogine 1984). Without forgetting the roots of Merleau-Ponty's phenomenology, with the overcoming of the principle of objectification from which the very idea of 'complexity' derives (Merleau-Ponty 2013).

Merleau-Ponty goes beyond the representational paradigm, exemplified by the figure of the chiasm, in which 'external' and 'internal', mind and world are not separate but, on the contrary, inextricably interpenetrated (Merleau-Ponty 1968, 2003, 2013).

From the point of view of cognitive science, this involves overcoming a neuro-centric paradigm in favour of an embodied and extended paradigm, referred to in the literature as the '4E' approach to cognition. According to this new paradigm, cognition occurs not only in the brain but is also Embodied, Embedded, Enacted and Extended and is realized in extracranial processes and structures (Carney 2020).

However, the constellation of the antireductionist front is much broader, both in the philosophical and scientific spheres and involves authors such as Wiener (Bitbol 2012; Chalmers 1996; Von Foerster 2003; von Foerster 2013; Bitbol 2021). In this perspective, conceiving the brain as the sole repository of cognition is reductive. Embodied cognition is an interdisciplinary field of research involving various views on cognition, from psychology to neuroscience, to philosophy. This theory, supported by George Lakoff and Mark Johnson (Lakoff and Johnson 2008; Varela 1986; Clark 2023; Gallagher 2017; Damasio 2010; Thompson 2007; Thompson and Stapleton 2009; Moran et al. 1976), argues that cognition depends on factors 'external' to strictly cerebral activity, as it is integrated with the body dimension and with the external environment. According to the extended mind paradigm pioneered by Clark and Chalmers (1998), cognitive activity is not limited to the territory bounded by a neural network. The background that legitimizes this antireductionist perspective is what is known as 'complexity science' (Figure 2).

4.1 | The Circular and Recursive Dynamism (The Retroactive Loop)

Probably the most important concept introduced by the science of complexity is the so-called 'Complex adaptive system', commonly referred to as a 'multi-agent system', characterized by a mutual adaptability between environment and single agents through their multiple interactions for creative evolution and self-organization processes (Holland 1996). Each organization of a complex system recursively produces other organizations of hierarchically higher level systems (C. Craver, Tabery, and Illari 2024).

These are systems that are created through self-organization and evolution and are adaptive and flexible, just like the brain, whose parts can perform different functions, proving its plasticity.

In 'The Nature of Nature', Edgar Morin exposed the general systems view on life and society. The volume explains that the organization of all life and society consists in a simultaneous

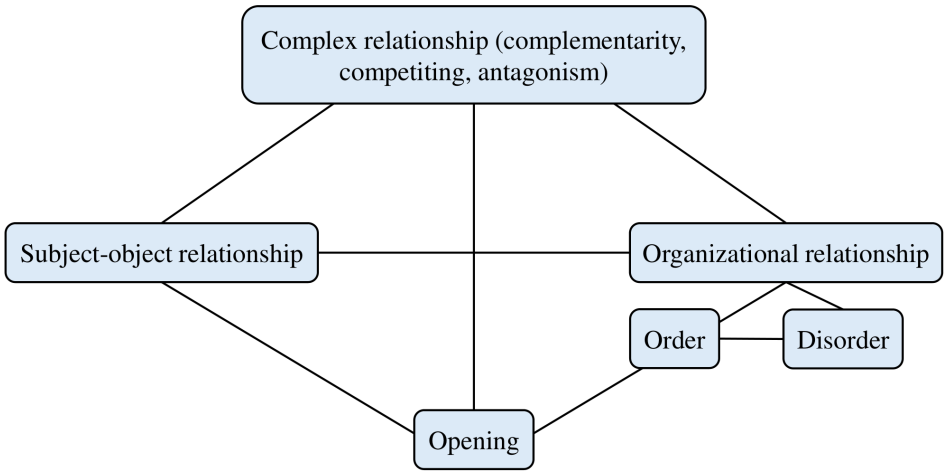

FIGURE 2 | Conceptual diagram illustrating the philosophical paradigm of complexity. A complex system consists of interconnected elements that dynamically interact (represented by connecting lines), giving rise to emergent properties. These emergent outcomes cannot be predicted solely by analysing individual components, highlighting the non-linearity and interdependence inherent in complex systems.

interplay of order and disorder. All systems, physical, biological, social, political and informational, incessantly reshape part and whole through feedback, thereby generating increasingly complex systems. For continued evolution, these simultaneously complementary, concurrent and antagonistic systems generate the continued life evolution (Morin 1992).

The philosophical importance of the complex theory of Edgard Morin is that it gives ontological dignity to concepts such as 'complexity' and 'chaos'. What distinguishes this new conception of the world is its holistic, systemic and multidimensional character.

Starting from 'Morin's dialogical principle', which provides for the inseparability of contradictory elements, we can conceive a complex phenomenon in which opposing elements interact creatively.

It follows that it breaks with the principle of linear causality, which leads us to the principle of the recursive ring, a generating ring in which effects are also producers of what produced them. If we look at the system in relation to its components considered in isolation or juxtaposed, the system presents itself as 'something more' for the new qualities and properties of the global unit itself (the 'whole'), the new qualities and properties emerging. From this perspective, therefore, the whole is more than the sum of the parties. It is, in fact, an 'emergence' compared with these (Morin 1992, 123).

The idea of 'emergence' is produced by the organization of the system; it means that the loop, a 'Recursive Organization and Reorganization', generates it.

The emergence represents a breakdown of two-way relationships between cause and effect, as the resultant does not exhibit a linear change in response to modifications of its parts. This shifts the perspective to a non-linear framework. In the context of cybernetic self-organization, a similar concept emerges in the relationships between systems and their elements, reflecting the Morinian dialogue between the whole and its parts.

Three interconnected categories of emergence are generally identified:

Property Emergence: When systems of objects reach a sufficient level of organizational complexity, genuinely novel (and often unpredictable) properties can arise at the level of the system as a whole.

Irreducibility of Emergence: Emergent properties are not only unpredictable but also irreducible to the lower level constituents from which they arise.

Downward Causation: Emergent properties, as higher level entities, exhibit genuinely novel causal powers that influence their lower level constituents in ways that cannot occur at the level of the constituents themselves. This phenomenon is also referred to as higher level or global *supervenience* (Morin 1992, 223–224–257).

There are two general theoretical approaches to studying emergent phenomena: the synchronic and the diachronic.

The synchronic approach examines the emergent properties of a system in its present state, without considering how these properties or the system itself came into existence or evolved over time.

The diachronic approach focuses on the development of emergent properties over time as part of an evolutionary process, a concept referred to as 'evolutionary emergence'.

As Morin says:

> Emergence has something relative (to the system that produced it and on which it depends) and something absolute (in its novelty) and we must consider it from these two apparently antagonistic points of view. Every organizational interrelation supposes the existence and the play of attractions, affinities, possibilities of bonds or of communications between elements or individuals. (Morin 1992, 80–182)

Co-organization is fundamental; it is involved by 'recursiveness' itself. This ring takes on a spiral shape, Morin observes, which modifies the laws of recursive relations: 'evolution determines selection to the same extent that it is determined by it'. Evolution, therefore, is not only an effect, a product, but also a cause and factor of 'co-production of the ring' (Morin 1992, 121).

For Morin, there is only one method capable of accompanying the rediscovery of the organizational complexity of reality. Escaping from the *'adaequatio rei'*, the essence of the nature resides in the organization that allows each system to regenerate itself and prevent degeneration.

The parts of complex systems interact and reciprocally influence each other, leading to emergent phenomena. A complex Organization is active and fundamentally recursive. Besides, there is also 'the researcher's permanent self-critical reflexive recursion of himself' (Morin 1992, 183–184).

Disorder within the organization plays both an ontological and a methodological role. The complex organization of the brain does not coincide with an eternal and immutable, causal-linear order; it coincides instead with autopoiesis, with a totality that can be investigated with the logic of 'RE-cursiveness'.

The core idea is that the parts are mutually interactive and complementary, engaged in a radical and continuous dialogue that integrates competition, antagonism, complementarity, and uncertainty within a constantly evolving logic. Morin speaks about 'Co-organization', of 'organizing eco-cooperation', between the parts and the whole of a system, the whole is together (Morin 1992, 202–204).

The principle of the recursive loop or 'recursiveness' goes beyond retroactivity or feedback loops understood in neuroscience. Recursion is not merely a retroactive loop but a process that is fundamentally self-sustaining and self-nourishing. It represents a dynamic in which an initial state becomes final while remaining initial, and a final stage becomes initial while remaining final. In this context, recursion is a process where the effects or products of a system are indispensable for its own regeneration and continuation, creating a self-eco-causal loop rather than a simple feedback loop (Morin 1992, 120–121).

5 | The Retroactive Loop to Reconsider the Synapses–Glia Interactions in the Brain

Our aim in this article is to propose a practical application of the 'Theory of Complexity' and in particular the principle of 'circular and recursive dynamism' of Morin for the study of neuron–glia interactions in the brain using as an example the multipartite synapse system.

Says Morin that 'Beyond Holism and Reductionism there is the Relational Circuit'. Neither the description nor the explanation of a system can be given at the level of the parts, conceived as isolated entities, tied only by actions and reactions. The analytical decomposition into elements also decomposes the system, whose rules of composition are not additive but transforming. Morin says that 'Active organizations of systems called "open" insure the exchanges, the transformations which nourish and effect their own survival' (Morin 1992, 196–199).

Based on the above morinian principles, we propose a new 'Complexity Observation Grid' as a complementary method of observation that can help neuroscientists to better interpret their experimental results and plan, in a more efficient way, the experiments, without using a reductionism pattern.

5.1 | The Complexity Observation Grid

The complex organization of multipartite synapses in the brain does not align with a fixed, linear causal order. Instead, it corresponds with autopoiesis, encompassing a totality that can be examined through the logic of 'RE-cursiveness', interretroactive components, element complementarity and the principle of radical '*dialogicity*'. This principle integrates competition, antagonism, complementarity and uncertainty within a continuously evolving logic. To know is to separate and bind together. The Complexity Observation Grid, based on the possibility of making terms that refer to each other interact, would create a complex knowledge, a knowledge not based linearly on inputs and outputs but on the search and observation of interactions and emergence.

Complexity Observation Grid is a mindset, a philosophical tool that provides a conceptual framework, a way of thinking and a way of seeing the world of scientific experiments.

5.1.1 | Recursiveness

Recursiveness arises from the inter-relationship, interaction and inter-retro-connectivity of elements within a system and between a system and its environment. It is therefore associated with the intricate inter-twining or inter-connectivity of elements within a system and between a system and its environment within a process.

5.1.2 | Coevolution

A way of describing coevolution is that the evolution of one domain or entity is partially dependent on the evolution of other related domains or entities. This relationship means that coevolution between entities can only take place within a sort of ecosystem.

The parts of a system are not distinct but are interconnected and reversible.

5.2 | Operationalizing the Theory: The RE-CO Grid

The concepts and principles introduced above should not remain purely theoretical speculations. A general programming paradigm founded on the fact that in our traditional means of understanding, explanation and experimental prediction, we must add the direct study of the emergence of a system like the brain, using a paradigm like 'RE-CO scheme' or grid, of observation.

When we approach whatever experiment we must observe the links, the interreactions of the parts and elements in the brain synapses, we might take into consideration the real 'process', the generative loops among the system and the subsystems.

Using this paradigm by RE-CO grid, which means recursiveness and coevolution grid, we can avoid philosophically 'cut off' part of the reality itself, and we can otherwise assume the 'making sense' of the process.

'RE-CO' grid in steps:

1. *The systemic principle*: impossible knowing the parts without knowing the whole.
2. *The hologrammatic principle*: not only the parts are in the whole, but also the whole is inscribed in the single part.
3. *The principle of the retroactive ring*: the cause acts on the effect and the effect acts on the cause.
4. *The dialogical principle*: conceiving a complex phenomenon it is necessary to assume the inseparability of contradictory notions and concepts.
5. *The principle of autonomy/dependence*: autonomy is inseparable from the environment. The knowing subject or observer is reintegrated into the research process.

The 'RE-CO' grid is a grid of recursiveness for 'non-simplification' through the search for

- Links between the parts of a system

- Dynamic joints

- Solidarity between the parties

- Interdependencies

- Implications

- Two-way relationships

- Two epistemological prefixes: the 'RE-' and the 'CO-'

We propose the use of the 'RE-CO' grid as a pre-experimental tool for neuroscientists, starting with the example of the neuron–glia interactions at the synaptic level. The aim is to better plan the experimental procedures in terms of the models and approaches to describe the synaptic molecular mechanisms, as detailed in the first part of this review.

Following the simple logical framework proposed in the RE-CO grid principles and applications, we aim to standardize the theoretical plan of a typical experiment, considering the models and techniques used to address a specific question.

5.3 | RE-CO Application at the Multipartite Synapse

In this section, we outline a step-by-step reasoning framework to address critical elements when planning experiments aimed at elucidating glia-neuronal interactions at the synaptic level in both physiological and pathological contexts. This framework incorporates the Morinian recursiveness theory of complexity, ensuring that each experimental design is approached in an antireductionist manner. This approach acknowledges the inherent complexity of the synaptic system and the experimental process itself.

Below are examples illustrating the application of the RE-CO framework for studying neuron–glia interactions at multipartite synapses, based on the scientific literature discussed earlier in this manuscript (Figure 3).

1. Complexity of the Model

- Is my model sufficiently complex to accurately describe the interactions and their effects?

Example: When investigating specific synaptic mechanisms, such as the modulation of neuronal activity by glial activation (e.g., ATP or glutamate signalling), does the model account for the complexity of brain parenchyma and interregional connections?

- -Does my model include all relevant mediators between neurons and glia? What elements might be missing?

Example: Does the model incorporate mediators like ATP and GABA that are naturally released by the experimental system?

2. Consideration of Multiple Cell Types

- Is the effect we are describing specific to only one cell type, or might other cell types also be involved?

Example: When studying astrocytic signalling, should we also consider the role of microglia, particularly in studies involving ATP?

3. In Vitro, Ex Vivo and In Vivo Considerations

- Are we considering whether the glia–neuron effects observed are specific to the experimental conditions?

Example: Ex vivo brain slices may exhibit different concentrations of glia and neuron mediators compared to in vivo conditions (e.g., glutamate and GABA). Pharmacological responses may also vary between these conditions.

4. Different Experimental Models

- Does the choice of experimental model (animal vs. human) influence neuron–glia interactions?

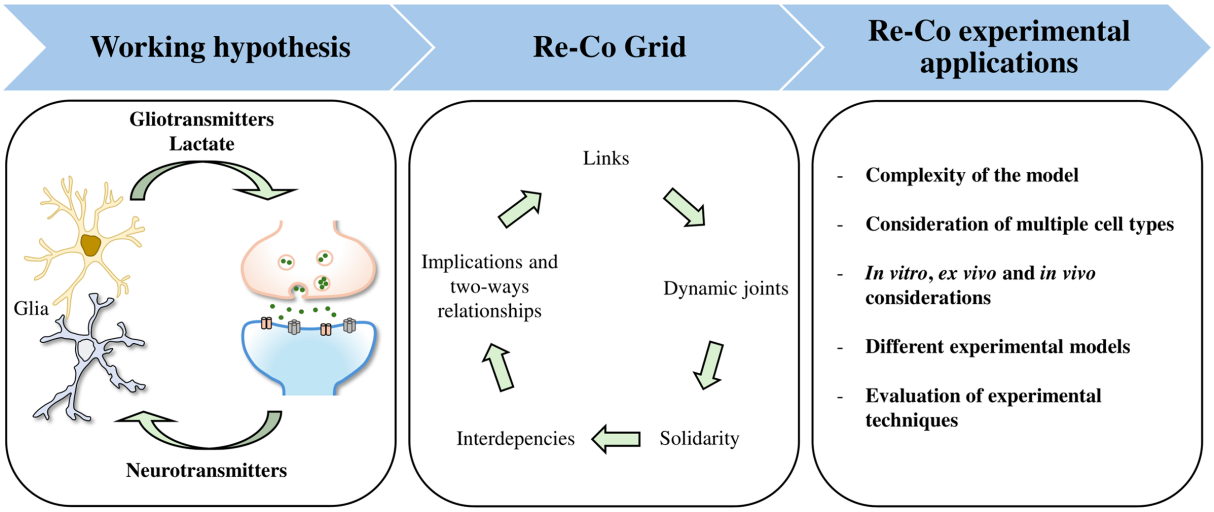

FIGURE 3 | Application of the RE-CO framework to neuron–glia interaction hypotheses. This illustration depicts the application of the RE-CO framework to the study of neuron–glia interactions at multipartite synapses. The conceptual scheme is structured into three key steps: Working Hypothesis emphasizes bidirectional interactions between neurons and glial cells via gliotransmitters, lactate and neurotransmitters, under both physiological and pathological conditions. RE-CO grid highlights the dynamic relationships, interconnections and cooperative processes governing neuron–glia interactions. Experimental Applications incorporates the complexity of experimental models; accounts for multiple cell types; integrates in vitro, ex vivo and in vivo approaches; and evaluates a range of experimental techniques. This framework provides a structured approach for investigating the multifaceted nature of neuron–glia interactions within complex neural systems.

Example: Purinergic activation of microglia (e.g., ATP) and cell motility can differ between human and animal brains (Milior et al. 2020) potentially affecting neuronal activity in distinct ways.

5. Evaluation of Experimental Techniques

- When describing general glia–neuron mechanisms, are we using a reductionist approach without considering the impact of specific experimental techniques?

Example: Live imaging techniques, such as astrocytic calcium imaging, may be influenced by factors like heating and light conditions of the laser microscope, which may, in turn, affect synaptic activity. This introduces potential confounding issues about the mechanisms behind the multipartite synaptic functions.

6 | RE-CO Application for an Antireductionist Approach in the Neuroscientific Experimental Procedures

The application of the RE-CO framework prior to conducting experiments underscores that neuron–glia interactions cannot be fully understood in isolation. Instead, it highlights the importance of examining how these interactions integrate to regulate brain function. We propose utilizing the RE-CO approach to address the previously mentioned key questions, which represent fundamental objectives in neuroscience research (Figure 4).

6.1 | Understanding Neural Networks

The RE-CO approach encourages viewing the glia–neuron interactions as an interconnected and dynamic network, rather than focusing exclusively on isolated molecular or cellular mechanisms. The application of the RE-CO can provide a better theoretical understanding of how changes in one component between glia and neurons at the synaptic level may affect the entire system.

6.2 | Exploration of Emergent Properties

The use of the RE-CO encourages exploring how complex interactions between neurons and glia contribute to global brain function properties in physiology and pathology. Emergent properties such as memory, learning and brain adaptability cannot be explained only by the molecular mechanisms of individual cell type but as a coparticipation of several cells.

6.3 | Implications for Research and Therapy

Instead of targeting individual components, it may be more effective to develop therapeutic approaches that consider the integrity and complexity of the nervous system as a whole. The ROG application in the study of neuron–glia interactions can improve the way researcher look for and propose new neurological therapies considering the complex interactions between different cell types.

The RE-CO grid in the study of neuron–glia interactions promotes a systemic and integrated view of the nervous system, emphasizing the importance of considering complex interactions and emergent properties within their natural context for drug discovery.

7 | Discussion

The emergence of the ‘science of complexity’ in the 1980s represented a significant shift in scientific and epistemological thought, challenging the traditional Newtonian paradigm

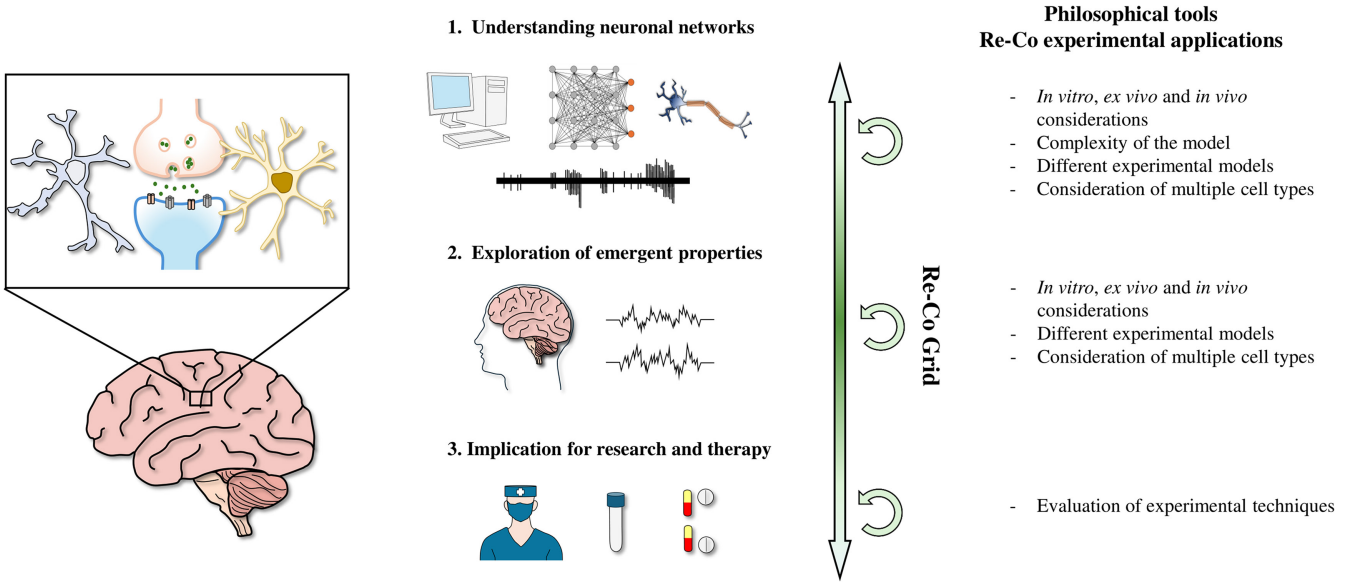

FIGURE 4 | The RE-CO grid workflow: A holistic approach to neuronal networks and therapeutic research. This figure illustrates how the RE-CO grid framework provides an antireductionist theoretical approach to understanding neuronal networks, investigating emergent brain properties and advancing therapeutic research. It underscores the crucial role of philosophical tools—such as retroactive loops—in achieving a comprehensive understanding of neuron–glia interactions. On the left, the primary biological research objectives are outlined: deciphering neural network dynamics, exploring emergent brain properties and translating insights into research and therapeutic applications. On the right, the RE-CO process is depicted, emphasizing iterative, dynamic and interactive retroactive loops across these domains. By integrating these conceptual frameworks, this approach ensures that experimental designs move beyond reductionist methodologies, fostering a holistic and systems-level understanding of neuron–glia interactions.

that emphasized reductionism and determinism. This new approach, deeply influenced by cybernetics, chaos theory and evolutionary biology, prioritizes the study of systems as interconnected, adaptive and emergent entities. Philosophers and scientists like Edgar Morin, Ilya Prigogine and Gregory Bateson have been central in framing this discourse, arguing for a holistic systemic view that recognizes the interdependence of parts and wholes.

Merleau-Ponty's phenomenology and its rejection of objectification resonate with the principles of complexity, particularly in how mind and world are seen as inextricably intertwined. This perspective has been influential in cognitive science, giving rise to the '4E' approach (Embodied, Embedded, Enacted and Extended cognition), which argues that cognitive processes are not confined to the brain but are distributed across the body and environment.

In neuroscience, this shift away from a neuro-centric view has profound implications. Traditional models that isolated neurons or glial cells are increasingly seen as inadequate for capturing the complexity of brain function. The multipartite synapse model, for example, recognizes the active role of astrocytes and microglia in modulating synaptic activity, reflecting the principles of complexity science.

The multipartite synapse model, which extends the traditional view of synaptic interactions to include not only neurons but also glial cells, presents a complex and dynamic picture of neural communication. This model challenges the classical, linear understanding of synaptic function by introducing concepts such as autopoiesis, interretroactivity and radical '*dialogicity*'. These concepts emphasize the non-linear, self-organizing and interactive nature of synaptic processes, where multiple cell types and signalling mechanisms contribute to the overall function of the brain.

One of the key insights from the multipartite synapse model is the recognition that synaptic interactions are not static but are continually shaped by the reciprocal influences of neurons, astrocytes and microglia. Glia, traditionally seen as passive immune cells, are now understood to play an active role in sensing neuronal activity and actively modulating synaptic functions. Their ability to rapidly respond to changes in the neural environment and engage in bidirectional communication with neurons underscores their importance in maintaining synaptic homeostasis and responding to pathological stimuli.

Morin's concept of 'recursive organization' underscores the dynamic, circular processes inherent in complex systems, where cause and effect are interdependent and continuously evolving. This idea is particularly relevant to understanding the brain's plasticity and the adaptive nature of neuron–glia interactions. The 'RE-CO' grid, proposed in this article, serves as an example of a practical application of complexity theory to experimental neuroscience. It offers a structured theoretical approach for researchers to consider the interconnectedness and emergent properties of the systems they study, encouraging a move away from reductionist methodologies.

The application of the RE-CO framework to studying multipartite synapses offers a shift in how we approach experiments investigating neuron–glia interactions. By emphasizing

complexity and antireductionism, this framework provides a more holistic view of synaptic dynamics and the intricate interplay between neurons and glia.

Specifically in this manuscript, we target a form of methodological reductionism, which is grounded in an ontological acknowledgment of the intricate and dynamic nature of the processes being studied.

Although we embrace methodological reductionism as a pragmatic scientific strategy—analysing the 'whole' by examining its constituent parts—we firmly maintain an antireductionist stance in both ontological and epistemological terms. By affirming an antireductionist vision, we distance ourselves from conceptual, causal and ontological reductionism, which regard the whole merely as the sum of its parts. Instead, we advocate for an approach that prioritizes understanding the self-organizing relationships between the whole and its parts. This approach rejects the principle of disjunction or separation and replaces it with a principle of distinction that seeks to establish meaningful relationships.

Methodological reductionism, as a scientific strategy, can be valuable when it is integrated with multidisciplinarity and a 'processual' approach. '*Processuality*' is a fundamental concept, as it begins with the notions of 'change' and 'happening'. This perspective is inherently relational and organic, but it avoids adopting an absolutist or overly holistic stance. Instead, it allows for a dynamic understanding of systems and their interactions.

In neuroscience, as in other scientific domains, a shift in approach is currently underway to better explain the complex phenomena of the human brain. The traditional 'pure localization' paradigm—associating specific brain structures with fixed mental functions—is increasingly being abandoned in favour of approaches that recognize the brain's complexity (Sultana et al. 2024). Higher cognitive abilities, such as memory, language, attention and consciousness, are now understood to arise not from isolated brain regions but from the integrated activity of multiple networks, each involving distinct parts of the brain with specialized functional roles (Johnson 2011). This more nuanced and relational perspective is essential for advancing our understanding of the human brain's intricate operations.

7.1 | The Reductionism in Neuroscience Research

Although some areas of neuroscience can clearly be characterized as reductionist, it is essential to acknowledge that the degree and type of reductionism vary across different subfields. Reductionism in neuroscience often involves breaking down complex phenomena into simpler components, such as studying molecular and cellular mechanisms, neural circuits or individual brain regions. For example, molecular neuroscience frequently employs methodological reductionism to understand the roles of specific genes, proteins and signalling pathways in neural function and dysfunction (C. F. Craver 2007). Similarly, neurophysiology often isolates individual neurons or small circuits to examine their contributions to broader neural networks.

However, not all areas of neuroscience rely exclusively on reductionistic approaches. Cognitive neuroscience, for instance, increasingly emphasizes the integrated activity of large-scale networks to explain complex phenomena such as consciousness, memory and decision-making (Pessoa 2014). This field often adopts systems-level approaches that prioritize interactions between multiple regions rather than isolating individual components. The study of neural plasticity, a domain where cellular and molecular processes interact with whole-brain systems, also illustrates the limitations of strict reductionism (Feldman 2009).

A gradient of reductionism thus exists within neuroscience, with some domains leaning more heavily on reductionistic methodologies and others adopting holistic or integrative frameworks. For example, although molecular and cellular neuroscience can often be viewed as reductionistic, fields like systems neuroscience and computational neuroscience balance reductionism with emergentist perspectives, acknowledging that higher order brain functions cannot always be fully understood by examining individual components alone (Bechtel and Richardson 2010).

This gradient highlights the need for nuanced approaches that bridge reductionistic and integrative methodologies, depending on the research question. Reductionism provides detailed insights into the mechanisms underlying neural function, but a comprehensive understanding of the brain and behaviour requires acknowledging the complexity of interactions across scales and levels of organization.

In some cases, reductionism has played a pivotal role in advancing neuroscience by enabling the dissection of complex neural phenomena into manageable components, thereby yielding profound insights into brain function and dysfunction. Historically, one of the most significant examples of reductionism in neuroscience is the Hodgkin and Huxley model of the action potential. By studying the squid giant axon, Hodgkin and Huxley (1952) developed a mathematical model describing how ionic currents generate and propagate electrical signals in neurons. This reductionist approach, focusing on individual ionic mechanisms, laid the foundation for modern electrophysiology and earned them the Nobel Prize in 1963.

Another notable example is the discovery of long-term potentiation (LTP) as a cellular mechanism underlying learning and memory. Bliss and Lomo (1973) demonstrated that repetitive stimulation of specific hippocampal pathways could enhance synaptic strength, a finding that revolutionized our understanding of synaptic plasticity. By isolating specific neural circuits and examining molecular and cellular changes, researchers were able to link these mechanisms to cognitive processes such as memory formation (Malenka and Bear 2004).

Similarly, reductionism facilitated the identification of dopamine as a critical neurotransmitter in reward and motor systems. Early research on Parkinson's disease demonstrated that dopamine depletion in the basal ganglia was a key factor in motor dysfunction, leading to breakthroughs in treatments such as levodopa therapy (Carlsson 2001). This reductionist perspective, which focused on specific neurotransmitter systems, has since expanded to encompass broader neural networks involved in motivation and behaviour.

These historic examples illustrate how reductionism, when appropriately applied, can provide a foundation for understanding complex brain functions. Although modern neuroscience increasingly integrates reductionist approaches with systems-level perspectives, the value of reductionism in generating foundational insights remains undeniable.

7.2 | Complexity of Experimental Models in Neuron–Glia Interactions: The RE-CO Grid

However, especially for neuron–glia studies, the RE-CO framework highlights the need for experimental models that accurately reflect the complexity of the brain's synaptic systems. Traditional models often simplify these systems, potentially overlooking critical aspects of synaptic interactions. For instance, models that do not incorporate the full spectrum of glial and neuronal mediators may fail to capture essential dynamics, such as the modulation of neuronal activity by ATP or glutamate signalling. This limitation underscores the importance of developing and utilizing models that incorporate the multifaceted nature of brain parenchyma and interregional connectivity.

7.3 | Multicell-Type Interactions

Recognizing the roles of multiple cell types is crucial for understanding the full scope of neuron–glia interactions. The RE-CO approach advocates for the inclusion of various cell types in experimental designs, such as considering the interactions between astrocytes and microglia. For example, studies focusing solely on astrocytic signalling might miss significant contributions from microglia, particularly in processes involving ATP signalling. This perspective encourages a broader view that can reveal more nuanced mechanisms underlying synaptic function and pathology.

7.4 | In Vitro, Ex Vivo and In Vivo Considerations

The differences between in vitro, ex vivo and in vivo conditions are critical for interpreting experimental results. As highlighted by the RE-CO framework, each experimental setting offers unique insights but also comes with limitations. Ex vivo brain slices, for example, may not fully replicate the in vivo environment, potentially leading to discrepancies in mediator concentrations and pharmacological responses. Acknowledging these differences helps in understanding how findings from one model might translate to more complex biological systems.

7.5 | Influence of Experimental Models

The choice between animal and human models can significantly affect the results of neuron–glia interaction studies. Variations in microglial activation and cell motility between species can lead to differences in how neuronal activity is regulated. This aspect emphasizes the need for careful selection of experimental models and consideration of species-specific differences when interpreting data and translating findings to human conditions.

7.6 | Impact of Experimental Techniques

The techniques used to study glia–neuron interactions can introduce additional variables that affect the outcome of experiments. For instance, live imaging techniques can be influenced by factors such as light conditions and temperature, which may inadvertently alter neuronal activity. Recognizing and addressing these technical factors is crucial for ensuring the validity and reliability of experimental results. This insight also underscores the importance of refining experimental methodologies to minimize confounding effects.

In conclusion, the application of the RE-CO grid in neuroscience promises to deepen our understanding of brain function by emphasizing the importance of systemic interrelations, coevolution and the non-linear dynamics of synaptic interactions. This approach not only aligns with contemporary philosophical trends but also offers a robust framework for designing experiments that reflect the true complexity of neural systems.

8 | Perspectives

Looking ahead, the integration of the RE-CO framework into experimental design offers several promising avenues for advancing our understanding of synaptic interactions. Future research could benefit from the following:

8.1 | Developing Advanced Models

There is a need for sophisticated models that more accurately represent the complexity of the brain's synaptic systems, incorporating a wide range of mediators and cell types. Innovations in modelling techniques could provide deeper insights into the multifaceted nature of neuron–glia interactions.

8.2 | Cross-Species Comparisons

Comparative studies between different species, including humans, can reveal critical differences and similarities in synaptic mechanisms. These studies will enhance our understanding of how findings from animal models apply to human physiology and pathology.

8.3 | Refining Techniques

Advances in experimental techniques, such as improved imaging methods and more precise pharmacological, genetics tools, can reduce the impact of confounding variables and improve the accuracy of data. Ongoing refinement of these techniques will be essential for capturing the dynamic nature of neuron–glia interactions.

8.4 | Integrative Approaches

Combining multiple methodologies and experimental models can provide a more comprehensive view of synaptic function and pathology. An integrative approach that considers various levels of complexity and technical constraints will likely yield the most robust and insightful findings.

In conclusion, the application of the RE-CO framework represents a new philosophical tool applied for the study of neuron–glia interactions. By addressing the complexity and embracing a multifaceted approach, researchers can gain a deeper understanding of the fundamental processes underlying synaptic function and dysfunction. Continued exploration and refinement of these ideas may be useful for advancing both basic neuroscience and clinical applications.

We hope that following the RE-CO grid will help neuroscientists improve the replicability of their experiments by accounting for variables that often hinder the successful reproduction of experimental data in other laboratories.

9 | Philosophical Considerations Applied to the Scientific Research Process

Looking ahead, we must acknowledge that 'non-linear' models of self-organization describe only a part of the features of emergence. A truly complex system, such as the brain, also exhibits hierarchical and multilevel aspects.

The distinction between traditional problem-solving and recursive/coevolutionary approaches lies in the fact that in the

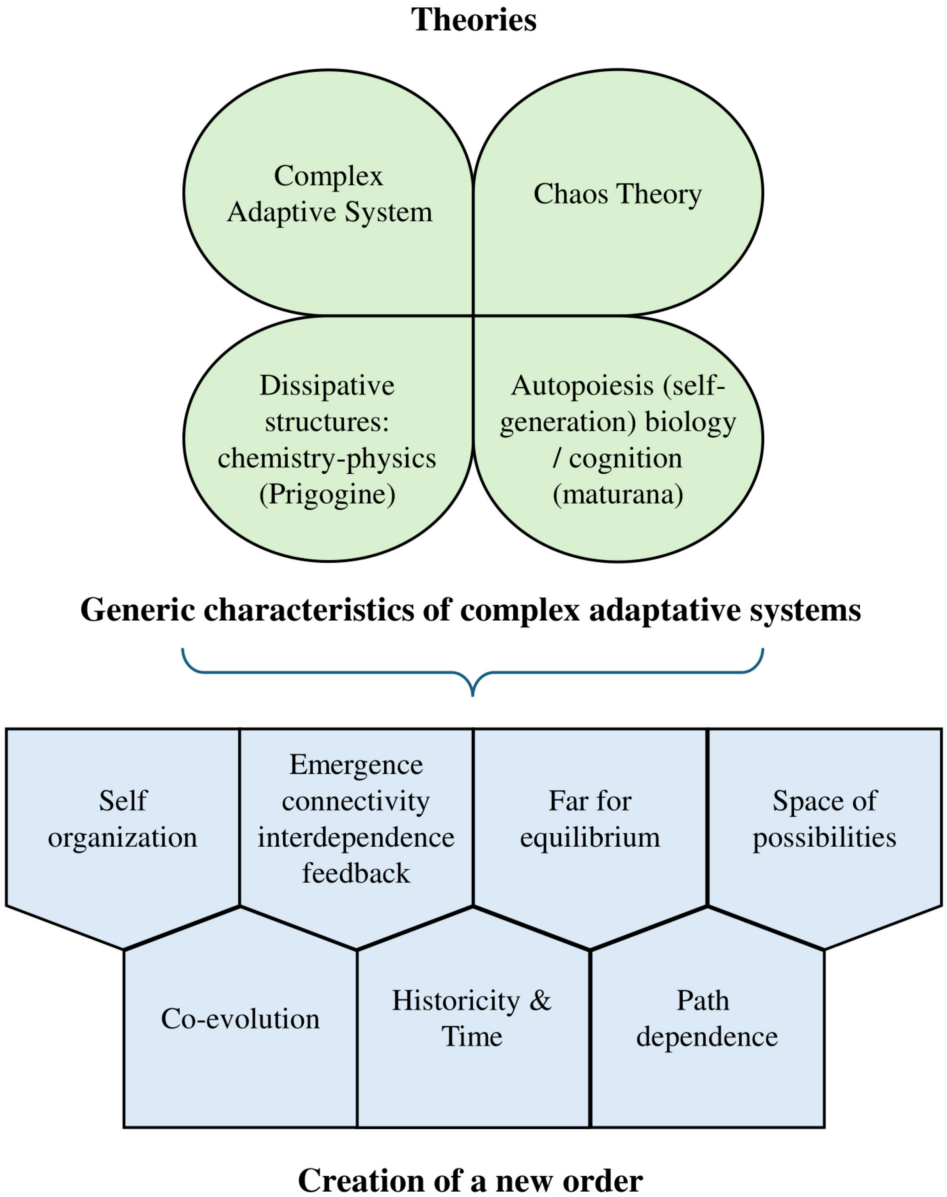

FIGURE 5 | Conceptual diagram of Complexity Theory summarizing the main theories and key characteristics of complex adaptive systems. It illustrates the theories contributing to complexity thinking and highlights fundamental features such as self-organization, emergence, connectivity, interdependence, feedback, far-from-equilibrium dynamics, exploration of possibilities, coevolution, and increasing returns.

latter, there is no definitive solution. A system is never optimally adapted to its environment because the process of evolution continually alters the environment, necessitating ongoing adaptation (see Figure 5). Each 'goal' within the process can be viewed as a subgoal of a broader, more distant goal, which in turn serves as a subgoal of another, and so forth. Thus, these 'subgoals' become crucial features of the process. The theory of self-organization might be based on an extension of this concept: 'relational closure'.

Laboratory experimentation must increasingly move away from mere modelling and simplification, shifting towards more interpretative, multidimensional and interdisciplinary approaches (see Table 1). 'Recursiveness' is central to this approach, describing a theory of predictability, reversibility and temporal order. The radical 'RE' becomes an epistemological and paradigmatic concept, representing a new way of thinking and analysing reality, which is informed by interactions, emergent phenomena, disorders and reorganizations. This approach abandons the simplifying and reductionist perspective of classical science.

In addition to 'Recursiveness', Morin introduces another epistemological prefix: 'Co-evolution/organization'. The concept of recursion does not replace the idea of feedback but rather provides it with a fundamental organizational foundation. Recursion, in terms of organizational praxis, logically entails self-production and regeneration (Morin 1992). Co-organization is integral, involving recursive processes. Morin observes that this process forms a spiral, altering the laws of recursive relationships: 'evolution determines selection to the same extent that it is determined by it'. Evolution, therefore, is not just an outcome or product but also a cause and factor in the 'co-production of the ring' (Morin 1992).

For Morin, there is only one method capable of facilitating the rediscovery of organizational complexity: moving beyond the *'adaequatio rei'*. The essence of nature lies in the organization that enables each system to regenerate rather than degenerate. The components of complex systems interact recursively, producing emergent phenomena. A complex organization is active and fundamentally recursive. Additionally, there is the 'researcher's permanent self-critical reflexive recursion' (Morin 1992). Disorder within the organization plays both an ontological and methodological role. The brain's complex organization does not align with an eternal, immutable, causal-linear order; rather, it aligns with autopoiesis and a totality that can be explored through the logic of 'RE-cursiveness'. The methodological tool from Morinian epistemology is a thought process that seeks connections, articulations, implications and interdependencies. Reality is no longer seen as a predictable, predetermined, and linearly causal mechanism but as a complex, irreducible, and historical organism, composed of interdependent parts that interact reciprocally, generating novelty and emergent phenomena. Organization is in a constant state of reorganization. Future research must consider multivariate analyses, random and chaotic elements and perform step-by-step process checks and operational interventions. Production and regeneration are key aspects. 'Production-of-self' refers to the retroactive/recursive process that continuously creates the system in an uninterrupted cycle fused with its existence. Regeneration denotes that the system, like any working system, generates increased entropy and thus requires generativity to avoid degeneration. Reorganization is related to the ongoing disorganization within the system (Morin 1992).

In the future, laboratory experiments will need to adopt a complexity approach, moving beyond reductionist simplification and pre-established models, as we resume in Table 1. Understanding complexity requires an effort to interpret and connect facts and elements, considering multiple dimensions and fostering interdisciplinary collaboration. The focus should be on 'ongoing processes' and their outcomes. By using multivariate analysis and managing randomness and chaotic elements, researchers can engage more deeply with the phenomena they study, moving beyond a detached or purely observational approach.

TABLE 1 | Proposed workflow for an antireductionist research using the principle of the Theory of Complexity principles.

Research and intervention using the Theory of Complexity			
Objective	**To explain**	**To understand**	**To change**
Type of research	*Laboratory experimentation*	*Hermeneutics*	*Experimentation + Intervention*
Treatment of complexity	- Simplification - Reduction - Modelling	- Articulation - Multidimensionality - Interdisciplinarity - Comparison between models	- In itinerary (process) verification as well as final (outcome)
Control method	- Control of randomness by statistical probability	- Multivariate analysis consideration of random and chaotic elements	- Direct monitoring of random incidences and intervention adjustments
Role of the researcher operator	- « Aseptic » observer	- Involved in interactions and deductions	- Actor of the change and of its verification together with the user

Source: Readapted from Di Nuovo (2014).

Author Contributions

M. Di Chiano: conceptualization, investigation, methodology, writing – original draft. **P. Milior:** conceptualization, investigation, methodology, writing – original draft. **Y. Poulot-Becq-Giraudon:** data curation, formal analysis, methodology, software. **R. Lanfredini:** conceptualization, investigation, methodology, supervision, writing – original draft. **G. Milior:** methodology, project administration, supervision, writing – original draft.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The figures supporting this review are available on Figshare at DOI: 10.6084/m9.figshare.28343849. Additional relevant materials, such as supplementary files, are provided in the repository to facilitate further research. Researchers interested in additional details may contact the corresponding author.

Peer Review

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