



On The Biophysical Complexity of Brain Dynamics: An Outlook

Nandan Shettigar, Chun-Lin Yang, Kuang-Chung Tu and C. Steve Suh *🕑

Nonlinear Engineering and Control Lab, Department of Mechanical Engineering, Texas A&M University, College Station, TX 77843-3123, USA; nandan90am@tamu.edu (N.S.); chunlin.yang@tamu.edu (C.-L.Y.); josepht0913@tamu.edu (K.-C.T.) * Correspondence: ssuh@tamu.edu

Abstract: The human brain is a complex network whose ensemble time evolution is directed by the cumulative interactions of its cellular components, such as neurons and glia cells. Coupled through chemical neurotransmission and receptor activation, these individuals interact with one another to varying degrees by triggering a variety of cellular activity from internal biological reconfigurations to external interactions with other network agents. Consequently, such local dynamic connections mediating the magnitude and direction of influence cells have on one another are highly nonlinear and facilitate, respectively, nonlinear and potentially chaotic multicellular higher-order collaborations. Thus, as a statistical physical system, the nonlinear culmination of local interactions produces complex global emergent network behaviors, enabling the highly dynamical, adaptive, and efficient response of a macroscopic brain network. Microstate reconfigurations are typically facilitated through synaptic and structural plasticity mechanisms that alter the degree of coupling (magnitude of influence) neurons have upon each other, dictating the type of coordinated macrostate emergence in populations of neural cells. These can emerge in the form of local regions of synchronized clusters about a center frequency composed of individual neural cell collaborations as a fundamental form of collective organization. A single mode of synchronization is insufficient for the computational needs of the brain. Thus, as neural components influence one another (cellular components, multiple clusters of synchronous populations, brain nuclei, and even brain regions), different patterns of neural behavior interact with one another to produce an emergent spatiotemporal spectral bandwidth of neural activity corresponding to the dynamical state of the brain network. Furthermore, hierarchical and selfsimilar structures support these network properties to operate effectively and efficiently. Neuroscience has come a long way since its inception; however, a comprehensive and intuitive understanding of how the brain works is still amiss. It is becoming evident that any singular perspective upon the grandiose biophysical complexity within the brain is inadequate. It is the purpose of this paper to provide an outlook through a multitude of perspectives, including the fundamental biological mechanisms and how these operate within the physical constraints of nature. Upon assessing the state of prior research efforts, in this paper, we identify the path future research effort should pursue to inspire progress in neuroscience.

Keywords: neuroscience; dynamic complex networks; spatiotemporal brain dynamics; synchronization; hierarchical structures; self-similarity; complexity

1. Introduction

The human brain is one of the most dynamically intricate networks molded by nature capable of performing a wide array of activities effectively and efficiently [1–4]. Operating on a high degree of complexity, brain dynamics consist of rapid reconfiguration of network states driven by interactions between network constituents to optimize temporal global evolution [5,6]. Constituents from the micro to the macro scale, such as neural cells, cluster to brain nuclei, and regions interplay with one another to compose an instantaneous,



Citation: Shettigar, N.; Yang, C.-L.; Tu, K.-C.; Suh, C.S. On The Biophysical Complexity of Brain Dynamics: An Outlook. *Dynamics* 2022, *2*, 114–148. https://doi.org/ 10.3390/dynamics2020006

Academic Editor: Christos Volos

Received: 31 March 2022 Accepted: 29 April 2022 Published: 5 May 2022

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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). dynamical form of the brain, which serves to interact with the environment [7,8]. Brain dynamics are unified across its spatiotemporal scales to work in concert to coordinate an instantaneous current representation while simultaneously maintaining active recollections and processing of prior experiences, along with evolutionary developed, primal, raw, emotional contexts, which can influence future trajectories and goals for the brain [9,10]. Constituent parts or subsystems of a network have unique responsibilities in contributing towards the overall time evolution of a network [11,12]. Thus, components of the brain cooperate and, in some cases, compete with one another from the micro to macro scales to direct and determine temporal evolution of the network's global behaviors [13]. Examples of these include neocortical modulation of amygdala activity to initiate higher-order cognitive regulation upon potentially fearful stimuli [14]. This interaction illustrates how activity produced by limbic regions (amygdala and associated areas), which provide primal emotional motivations such as fear, is regulated by contributions from the neocortex, which provides more complex forms of information manipulation, rendering higher cognitive thought to assess the initial appraisals of emotional response (such as fear) with more logic [15]. Furthermore, local activity from these regions are routed to one another via the thalamus, a relay center in the brain capable of coupling neocortical activity with a variety of localized subcortical structures. The resulting collaboration (or competition), sways global network trajectory towards a particular path [16]. The brain must simultaneously organize and process these various modes of information to construct an instinctual network system reaction, ensuring coherent brain behavior. Information is physically transmitted via configured patterns of electrophysiological neural activity. Upon accomplishing this, the brain can contextualize its network state within the time-varying environment. Learning from previous experiences, executing current actions, and preparing future expectations consists of these dynamical capabilities, enabling the brain to optimize the variety of possible opportunities posed by the time-varying environment, ranging from scavenging food to maneuvering social situations and assessing potential sexual partners.

Naturally, these tasks are highly multidimensional, necessitating the brain to operate with a substantial degree of complexity to not only participate but excel at such behaviors [17,18]. Furthermore, the brain itself is not a single, one-dimensional entity; it is a multidimensional macroscopic network ensemble consisting of smaller-scale constituent parts. Consequently, it is the cumulative interactions of these subordinate parts or subsystems that direct global brain behaviors towards replicating multidimensional forms that can recognize, interpret, and react by generating a desirable system action that influences or manipulates external factors, such as the environment or other constituents. Typically, these actions are not arbitrary but correspond to attempts to benefit the probability and conditions of an individual's survival (not excluding interactions/relations with external stimuli). To successfully coordinate this, neural architecture must be capable of filtering and translating relevant information from the environment in its own time-varying structure to comprehend and react to its surroundings [19–23]. Cytoarchitecture of the brain can represent this multidimensional variation of information over time within its own dynamical form by orchestrating the activity of ensembles of neural populations. Information is encoded within the unique firing patterns of such neural circuitry that represent individual recognition, understanding, and action in the environment. Thus, information representation capable of storing experiences and underlying motivations, as well as initiating actions, is embedded in the dynamical variation of unique patterns of electrical activity in the brain supported and modulated by neural, physiology providing stability for these dynamics [24].

Controlling the microstate configurations of neural biology corresponds to producing unique macrostate emergent behavior or representation of information by altering the interactions of unique patterns of local electrical activity, giving rise to diverse global behaviors. Thus, by fine tuning the coupling (interactions) between neural cells through various modes of plasticity (synaptic, axonal, and dendritic), microstate reconfigurations can modulate and refine macrostate behaviors on a variety of time scales corresponding to the speed of the various biological mechanisms [25]. The dynamical interplay of billions of neural cells coordinated by trillions of connections fosters effective and directed information transfer necessary for undertaking brain activities while balancing stability (to maintain a particular global form) and plasticity (being able to change, refine, and adapt global forms) [26]. The brain can control and steer the various possible configurations of a network to encode information pertinent to its conditions of survival.

Complex information can be expressed physically as a unique composition or pattern of dynamical behavior. In the brain, this composition consists of the unique temporal and spatial evolution of neural activity [27,28]. Illustrated in the time evolution and distribution of neuron action potential firing rates across the brain, neural cells (including glia) are responsible for directing this time-varying evolution at the microscopic scale. Furthermore, individual neuron action potentials do not operate in isolation but can influence or be influenced by other connected neural agents (individuals to population). If every single constituent were operating with disregard to its coupled neighbors, the emergence of higher-order patterned behavior would be difficult to produce. However, if agents can coordinate their behaviors, the collective effort is able to much better steer and influence global dynamics. Thus, neural individual agents act collaboratively to form higher-level neurodynamic rhythms [29]. In other words, the coalescence of individual neural firing mediated by connections between individual agents creates larger-scale brain rhythms commonly seen in global patterns, such as the bands of frequencies of electrical activity (corresponding to the rate and distribution of action potential activations of neurons) in the brain. Therefore, the form of higher order emergence such as local synchronization amongst populations of synchronized neural cells and global distribution of multiple synchronous modes (and sometimes asynchronous interactions) is essential to better define (and potentially control) overall network trajectory. Upon establishing certain preliminaries in Section 2, the dynamical aspects of such higher-order complexity will be reviewed in detail in Section 3.

Information, encoded in the rate and time evolution of electrical activity in the brain, is fueled by patterns of collaborative and competing frequencies of action potentials. Synchronous agents collaborate with one another to achieve higher levels of stability and influence while asynchronous dynamics compete with each other battling for influence in directing overall network directions. These are necessary to consider and filter all forms of relevant information to determine what action must be taken to optimize survival in the environment (by exciting and depressing respectively relevant and irrelevant information). A helpful analogy follows to aid clarity in how information representation is accomplished via patterns of neural activity: fundamental letters in the alphabet in particular configurations can produce a large variety of words, and these words enable configuration of further complex forms, from sentences to books, conveying information. Similarly, neuron action potentials are a fundamental building block for the dynamical repertoire of the brain, enabling higher-level information to be expressed as a unique patterned time evolution and spatial distribution of action potential firing. For example, raw sensory information is initially converted into electrical impulses capable of being transmitted to the central nervous system for further processing. Acquired sensory input is collected and translated into comprehensible information in the form of neural firing patterns. Broad information is then functionally segregated as specialized regions of the cortex process sensory stimuli to extract relevant features, such as visual and auditory information [30]. Upon sensory identification of the state of the environment information, the brain incorporates this information to form a global contextualization of the network regarding previous experiences and the current situation to determine a suitable response [31,32]. In other words, appraisal of external influences allows complex phenomena to be further dissected and understood with respect to internal network states. The physical medium for such information transfer is via activation of distinct patterns of neural activity.

From this, brain dynamical responses integrate discretized meaning into fluid understanding to formulate a suitable response. In other words, brain organization is structured to segregate information (assess sensory input) and integrate information, constructing an instinctual network system reaction, ensuring coherent and directed brain behavior [33]. This qualitative form is precisely quantified by the unique spatiotemporal spectra of frequencies in the brain representing information necessary to process input and contextualize said input with prior memories and evolutionary fine-tuned motivations to formulate a desirable system response observed and experienced in brain dynamics.

Qualitatively speaking, information contains meaning and can be physically represented [34]. Quantitatively, unique statistical signatures, such as variations of probability distributions (different standard deviations of the normal distribution), define degenerate forms, of which one can exist at an instant in time as a physical manifestation to encode information. The brain aims to generate unique statistical distributions to identify internal or external stimuli. Thus, to differentiate objects and scenarios and annotate meaning towards unique conditions, the brain must be capable of producing unique configurations that are able to differentiate one piece of information from the next while ensuring survival in a time-dependent environment. In other words, the same pattern of neural activity cannot be used to represent two different forms of information. Sufficient differentiation (based on the capabilities of the brain) between patterns of neural activity is necessary to respectively distinguish different phenomena. This includes wielding different dynamical states (spatiotemporal distribution of neural activity) in recognizing emotional states, varying from fear to hope to external scenarios, such as predatory or friendly encounters. From storing memories and executing actions to future planning and wielding subcortical motivations, distinct dynamical states are necessary to distinguish the aforementioned scenarios. Naturally, performing these tasks requires resources in the form of energy. This certainly has limitations, as physical energy constraints cannot create a limitless possible combination of stable configurations. With respect to energy conservation, hierarchical structures confer the efficient ability to organize the brain in a manner optimizing the finite number of relevant functional states the brain can morph into from stable physiological structure to produce wide-ranging adaptability [35]. Such architecture of complexity for dynamical configurations carries unique statistical signatures or characters at an optimal point between changing form and maintaining a current state. Therefore, hierarchical structures are conducive towards coordinating state transitions which minimize energy use and maximize the amount of relevant information representation. This can optimize information detection (input) and information presentation (output) from and towards the external environment (and internal states) in attempts to optimize survival. In seeking such unique dynamical configurations, self-similar structures emerge in the brain across scales to efficiently produce broadly adaptable dynamic behaviors. Self-similarity seeks to optimize network stability and plasticity by reinforcing network coupling configurations which correspond to efficiently being able to change or adapt dynamics while simultaneously maintaining reliable, stable forms in the face of adversity (battling a competitor for resources). In other words, a hierarchical structure confers efficient adaptability to the wide range of perturbations that may seek to disrupt the brain. Statistically self-similar (or fractal) structures can be found throughout the brain, conferring these necessary attributes and ensuring successful survival [36]. Qualitatively speaking, this can be thought of as producing the distinctive style or personality of an individual brain network in terms of the unique route an individual may choose to take in terms of isolating a single path towards a solution to a problem with many possible solution routes. In other words, this allows the brain to filter the variety of information present in the environment to direct energy towards relevant stimuli and consequently adapt in a way that attempts to minimize the action required to change form by holding certain fundamental signatures in the brain as statistically similar throughout its spatiotemporal scales. It is important to note that the brain's selected distinctive path may not necessarily be the absolute theoretical path of least action; however, it is a path chosen based on prior successes (through individual experiences or evolutionary fine-tuned configurations in neural architecture). Therefore, neural dynamics may not always perform perfect calculations which use the absolute

theoretical path of least action in performing tasks. However, it is noteworthy that despite its imperfections, fundamental architecture of the brain tends towards finding the optimal path of least action as this is the asymptotic limit for maximizing efficiency and optimizing survival within the environment. Millions of years of evolutionary pruning has likely eliminated network configurations which deviate significantly from such efficiency (as they were less likely to survive and reproduce due to lower levels of efficiency in neural information manipulation). The following paragraphs give an overview of tools and methods which can be used (and have been used) to better understand such neurodynamical complexity.

Concepts from statistical mechanics can define global dynamics by establishing relations between the microscopic and macroscopic state. A complex network is indeed a statistical mechanical system with energy distributed amongst constituents and their couplings. Therefore, the total energy can be defined by a probability distribution function, which changes over time with respect to the energy variation of individual ensemble constituents and their connections (consequently portraying the global state of the ensemble). The probability distribution of energy can be further defined using information entropy (or Shannon entropy) to describe the state of a complex network. Hence, stability or instability can be quantified with the corresponding information entropy and how it varies or fluctuates over time. Additionally, higher values of entropy correspond to a wider range of distribution, indicating less orchestrated collective behavior, whereas the opposite indicates more ordered ensemble dynamics gearing towards synchronized behaviors. Thus, information entropy can be used as a quantitative metric to assist bridging the character of global network states stemming from local behaviors. A further detailed description can be found in the referenced literature [37].

Brain dynamics are defined as the global neural processes that direct the network's evolution in time, commonly seen and experienced by the processing of sensory input and formulating a corresponding output [38]. These are typically observed in the change of the characteristics of the brain seen in the time-varying properties of the cumulative neuronal assemblies [39]. Experimental approaches observe this in the electrical activity of groups of neurons through electroencephalography (EEG) measurements or blood flow across brain regions through blood oxygen level dependency (BOLD) analysis via functional magnetic resonance imaging (fMRI) and how these properties change with exposure to new input [40,41]. It must be noted that these methods do not explicitly isolate component neuronal activity. For example, fMRI detects changes in blood flow related to brain activity (formally described as BOLD analysis). Naturally, as the brain evolves over time, resources are redistributed by altering blood flow, which is detectable through fMRI; however, the resolution of this observable change is not sufficient to delineate the firing properties and patterns down to the scale of individual neurons. In addition to limitations of spatial resolution, fMRI-centered BOLD analysis lacks the temporal resolution to identify the time evolution of a neural component's firing patterns at the millisecond scale [42]. On the other hand, it is also difficult to isolate component neural activity at sufficient resolutions using EEG, as the detected EEG waveform is a superposition of dynamic electromagnetic activity, including local field potentials generated through the cumulative ionic flux in and out of the cellular space [43]. Additional techniques using magnetoencephalography (MEG) detect changes in magnetic fields resulting from dynamic electrical currents produced in the brain from neuronal activities. These represent examples of observed changes in brain structure and function [44]. The interpretations of these methods have been refined over the years with the addition of advanced techniques [45,46]. Whereas concrete claims remain elusive due to a lack of temporal or spatial resolution, a commonly observed theme is that there is no stationary state of the brain [47]. For example, classical EEG experiments have framed brains as nonequilibrium systems along with the observation that unique patterns of EEG waveforms acquired from the olfactory bulb correspond towards information processing of specific odors [48]. These established studies make it apparent that the brain does not remain in a static configuration; its form changes to varying degrees over time. Therefore, the brain is fundamentally a nonstationary system without an equilibrium point

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that utilizes its biological capabilities to detect, interpret, and respond to the dynamical environment. Portions of this complexity are apparent through observable neurodynamic rhythms seen in EEG or fMRI recordings. Despite this recognition, the exact underpinnings of this substantial degree of complexity are among the core questions, ambiguities, and mysteries of modern neuroscience.

It must be recognized that significant understanding has been achieved through the earliest developments in neuroscience accomplished by Cajal and Broca, along with more recent undertakings utilizing the tools developed in network sciences, which have contributed to the development of a transdisciplinary perspective. Neuroscience research has been traditionally led by animal models, advanced neuroimaging techniques, brain tissue sampling, and separation methods [49–51]. These procedures have generated notable accomplishments, such as having a fundamental knowledge in identifying neuronal cell-mechanisms, structures, and functions, including dendritic and synaptic regulation, to identify and classify individuals, connections, and populations of neurons. Conventional approaches in neuroscience have led this progress; however, a comprehensive understanding of brain dynamical phenomena is still lacking in terms of how local and global cognitive mechanisms interplay simultaneously across multivariate scales. A transdisciplinary field of network sciences has emerged over the past 20 years in attempts to address complexity in the brain and other complex networks and has met with limited success, particularly in helping to realize that a transdisciplinary perspective is necessary to guide the next level of progress in neuroscience [52]. A brief review of the merits and limits of network sciences follows. Traditional network science has been spearheaded by graph theory, defining individuals in a network as nodes and their interactions as edgewise connections between nodes [53]. It is important to note that this is purely a mathematically driven formalism that is not necessarily driven by fundamental physical law. Small-world and scale-free network models have influenced the development of established network theories over the past 20 years [54,55]. For example, graph theory developments have been used to topologically describe networks and have been translated into anatomical and functional brain networks [56]. These are suited to capture small-world topology, such as highly interconnected hubs and modularity prevalent in the brain [57]. Additional topological properties of complex networks, such as hierarchies, centrality, and network hub distribution, have also been realized in this process [58]. Using serial reconstructions of electron microscopy, a complete connection matrix of the nematode C. elegans has been accomplished and described as a small-world network [59]. Furthermore, using combinations of physiological and anatomical techniques, multielectrode activity recordings have generated reconstructions of cellular networks in the neocortex, and diffusion tensor imaging has developed a map for cortical and basal brain gray matter areas [60]. The interplay of these methods has inspired a plethora of studies, models, and reviews [61-63]. These archetypes represent characteristics observed in networks under limitations. The assumptions underlying these limitations for small-world and scale-free networks must be considered when determining real-world applicability. For example, the network description is time-invariant, which neglects the dynamical elements inherent in all complex networks. Misrepresenting the dynamics can lower the accuracy of analysis at best or lead to catastrophic failure at worst. If the local interactions in a network are static, the global dynamics are adulterated and insufficient. Temporal networks are developed in attempts to compensate for this [64]. These models help represent the time-varying qualities of network structures, such as multilayer dynamics [65,66]. Whereas these help in developing tools better geared towards the dynamical aspects of complex networks, many of these methods still are plagued with the limited applicability of graph theory. For example, interactions represented by stationary edgewise connections between individuals lack the highly nonlinear features present in networks with diverse connections between individuals, groups, and large populations (composed of smaller groups and individuals) [67]. Misrepresentation of this fundamental nonlinearity and dynamics renders traditional methods inept for comprehensive analysis and control. Additionally, a pure mathematical representation of a network ensures quantitative precision; however, the current state of network sciences does not necessarily intertwine this foundation with fundamental physical laws, compromising its comprehensive accuracy.

Without dispute, these advancements have led to significant developments in understanding human brain physiology and function; however, the consensus in the literature and scientific community is that a comprehensive fundamental and intuitive understanding is still amiss for human brain phenomena. Progress is limited, as the complete characterization and interpretation of coupled neuron activity is still in its rudimentary stage, and the current practices are not able to capture a comprehensive picture of the ensemble of neurons within the human brain. This barrier prevents advanced progress in neuroscience research, pathology, and a general, intuitive understanding of brain functional processes. A prime reason for this is that these methods either do not have the resolution needed to analyze the detail within the brain or they do not comprehensively account for the inherent time-varying nature of the neurons and their respective dynamic connections. Additional impediments in this challenge are not only due to brain intricacy but also the sheer size and scale of complexity of the human brain. With around 100 billion neurons and 100 trillion connections, mapping out a comprehensive dynamic model of the human brain remains an elusive asymptotic goal with the current methodologies. Simply put, the conventional practices are not made to address the grandiosity present in brain dynamics described previously. Therefore, a new method from a unified perspective with the capability of analyzing the characteristics of the spatiotemporal spectra of dynamical brain physiology is imperative to attain a more comprehensive qualitative and quantitative understanding of neurological phenomena. It is our intuition that a truly modern outlook on the brain surveying and observing its biological evolution under the physical constraints and laws of nature is amiss. Therefore, in this paper, we aim to provide a transdisciplinary perspective on the human brain in the hopes to inspire truly universal, comprehensive studies upon the brain to help ignite the next stage of progress in neuroscience. In Section 2, Nonlinear *Biological Interactions*, we start off by describing the fundamental biological mechanisms, and in Section 3, Complex Global Multimodal from Local Nonlinear Interactions, and onward, we unify how electrophysiological structures can give rise to the nonlinear functional dynamical complexity prevalent in the human brain.

2. Nonlinear Biological Interactions

This section will express the nonlinear nature of local interactions and how these contribute towards global network properties. After this section, details on global network properties (including the form and structures of higher order neurodynamic complexity) will be reviewed in detail. For now, the global state of brain phenomena is a time-varying ensemble, consistently changing to different degrees in accordance with factors within and without. Thus, brain phenomena are consistently nonstationary to different degrees in accordance with different environmental perturbations navigated through nonlinear interactions, propelling a wide repertoire of dynamics [68]. The properties of these local interactions determine global form and function. Therefore, to better understand the macroscopic brain, one must begin first with the brain's auxiliary local interactions. As they cumulatively dictate global function, local interactions represent physical connections (or interactions) that deem the magnitude and direction of influence one agent has on another in a network and can be viewed as degrees of coupling [69]. These local interactions between connecting agents, regions, and subnetworks in the brain allow smaller-scale subsystems to coordinate with one another, composing coherent global forms by promoting coordinated local interactions, which engender stable global brain dynamics [70,71]. Thus, dynamical overall brain activity is nurtured through flexible configuration of local connectivity capable of generating a diverse variety of brain behaviors [72]. These include axonal architectures [73] with adaptive myelination [74], complex configurations of dendritic branching [75] and dendritic spine morphology [76], as well as the dynamic synapse [77], housing a multitude of pre- and postsynaptic mechanisms [78]. Importantly, each of these mechanisms is nonstationary and capable of dynamically influencing neural

interactions along a wide range of spatiotemporal scales. Thus, local interactions range from (1) microscopic interactions between individual neurons and glial cells to (2) interplay between clusters of nuclei in the brain to (3) mesoscopic relations between different regions of the brain, to highlight a select few (out of the many scales in the brain). The cumulation of these interactions, along with others not mentioned or yet to be discovered, is built to fine-tune connections between local brain regions operating on a variety of temporal and spatial scales. Due to these diverse factors of coupling, which can change on a variety of time scales, interactions are fundamentally nonlinear in the time-domain. Furthermore, nonlinearity, observed in the dynamical interactions amongst a wide distribution of neural frequencies, engenders highly nonlinear characteristics simultaneously in the frequency domain. Moving forward, these produce highly nonlinear characteristics in overall spatiotemporal brain dynamics, enabling the unprecedented level of network reconfiguration observed and experienced in the human brain. Thus, the simultaneous nonlinearity in the time and frequency domains elicits signature characteristics of chaos, which are essential for rapid reconfiguration of brain network states [79]. This topic is worthy of a detailed discussion for another review; however, for the context of this paper, it must be borne in mind that the level of global complexity in the brain is a product of its local nonlinearities at the fundamental level. In other words, the flexible nature of the connections (interactions) between individual parts of a brain network across its many scales and modes of operation provides the network with multiple routes to efficiently and effectively reorganize itself to detect, interpret, and react within its environment. The following will provide an overview of the biological mechanisms which steer the nature of local nonlinear interactions (culminating into complex global emergence).

2.1. Synaptic Plasticity

The following is a biological review of the various modes of connectivity and plasticity in the brain engendering nonlinear interactions. Although by no means exhaustive, our review represents a fundamental foundation with references that convey the necessary important takeaways, that is, the variety of biological mechanisms for connectivity and how they can change over time to support dynamic brain function. Synapses are not stationary over time. They are highly dynamic, entailing a variety of presynaptic and postsynaptic mechanisms capable of changing over time to fine tune the overall efficacy of synaptic transmission and corresponding synaptic strength [80,81]. Thus, synaptic plasticity confers the highest-resolution modus operandi in the brain for controlling and modulating interactions between constituents with the smallest temporal and spatial scales possible. Presynaptic plasticity includes modulation of presynaptic intracellular Ca⁺⁺ concentrations. This is primarily controlled by the function of voltage-gated calcium channels, which, when activated upon an incoming action potential, allow for the influx of Ca⁺⁺ inside the cellular presynaptic domain. Correspondingly, Ca⁺⁺ serves as a secondary messenger [82]. As calcium has a high reactivity with a variety of substances, it serves as the ideal secondary messenger to relay information. Thus, biological form manipulates Ca⁺⁺ reactivity to engender binding affinity upon different calcium-binding proteins. In the presynaptic cell, calcium forms a large signaling complex with SNAREs and associated proteins, triggering the binding of synaptic vesicles (containing neurotransmitters) with the membrane and consequent release of neurotransmitters within the vesicles [83]. Thus, regulation of voltage-gated calcium channels in the presynaptic domain has a significant influence on synaptic strength [84]. Furthermore, residual Ca⁺⁺ from prior activity can influence vesicle release [85]. The quantal release of neurotransmitters freely diffuses across the synaptic space. Diffusion of neurotransmitters implies that they stochastically bind upon receptors in the postsynaptic domain. Probability of neurotransmitter binding is dependent on total amount or concentration of neurotransmitters [86]. Larger amounts of released neurotransmitters result in a higher concentration of neurotransmitters in the synaptic space, corresponding to an increase in the probability of greater numbers of activated receptors, resulting in an interaction with greater magnitude between pre

and postsynaptic cells. Therefore, factors such as Ca⁺⁺ concentration modulate synaptic strength by influencing vesicle release and, correspondingly, the total quantal number of released neurotransmitters. Furthermore, within the presynaptic domain, a pool of readily releasable vesicles is maintained to, as the name suggests, be released at a moment's notice upon action potential arrival (triggering Ca⁺⁺ influx and consequent release of vesicles) to pervade the synaptic cleft with neurotransmitters. If these stores are exhausted by repetitive, higher-than-normal action potential firing, this may result in an overall decrease in the number of vesicles released, consequently reducing the concentration of neurotransmitters and vice-versa; factors that replenish or sustain a larger pool of readily releasable vesicles can increase the concentration of neurotransmitters [87]. Extrapolating from this, synaptic strength can be influenced by factors that control the concentration of neurotransmitters in the synaptic cleft. Thus, enzymatic machinery responsible for reducing the neurotransmitter concentration in the synaptic cleft to reduce the neurotransmitter activation time also influences the time course of synaptic strength [88]. This is an essential mechanism to terminate a signal, thereby offering additional degrees of flexibility in fine tuning synaptic dynamics.

Furthermore, there are multiple neurotransmitter reuptake mechanisms (or neurotransporters) responsible for removing neurotransmitters in the synaptic cleft [89]. These can also be utilized for future neurotransmitter release; thus, while influencing the concentration of neurotransmitters in the synaptic cleft, they can also alter the storage of readily releasable vesicles, consequently influencing the possible concentrations of neurotransmitters in the future. Reuptake can be undertaken by neurons and glia cells alike and is driven by neurotransporters, which can offer additional degrees of freedom to modulate synaptic connection strength by altering neurotransmitter concentrations [90,91]. Additionally, it must be recognized that non-neuronal glia cells (such as astrocytes [92]) can also modulate synaptic transmission [93,94]. Their importance, along with that of other types of glial cells, such as astrocytes, oligodendrocytes, and microglia, has recently come to light, and as research progresses, this further illuminates the importance of a variety of cells (having clear dynamical roles) previously considered to have relatively stationary roles in the dynamical ensemble of a neural network [95–97].

Synaptic strength modulation by postsynaptic mechanisms is accomplished by controlling the availability and number of receptors on the synaptic site. A greater number of available receptors results in a higher probability that freely diffused neurotransmitters (1) bind upon receptors and (2) elicit a post synaptic response. In other words, receptor amount and availability are directly correlated with synaptic strength. Therefore, postsynaptic plasticity mechanisms operate by modulating the properties of postsynaptic receptors. Receptor subtypes such as AMPAr and NMDAr play significant, dynamical roles in controlling factors such as receptor expression and availability [98]. Intracellular Ca⁺⁺ concentrations once again play a large role as secondary messengers in modulating the expression of receptors. CaMKII and calcineurin are two examples of calcium-binding proteins, where the former typically initiates phosphorylation, typically resulting in longterm potentiation (synaptic strengthening), whereas the latter initiates dephosphorylation events that often lead to long-term depression (weaking of synapses) [99,100]. Of utmost relevance to synaptic plasticity, the intracellular Ca⁺⁺ concentration regulates the expression of receptors. A higher Ca⁺⁺ concentration increases the probability of Ca⁺⁺ binding and activating protein units, resulting in AMPAr exocytosis [101]. A larger number of AMPAr results in a greater cumulative cross-sectional available area of receptors. Ergo, the flux of ions across the membrane multiplied by the cumulative greater cross-sectional area of the receptors (due to AMPAr exocytosis) results in an overall larger increase in postsynaptic potential, that is, a greater level of influence between neuron cells through a stronger degree of coupling [102].

NMDAr Mg⁺⁺ blockage and relief of blockage via membrane potential excitation are at the core of controlling the direction and magnitude of plasticity [103]. This is based on temporal correlation of presynaptic and postsynaptic neuron firings [104]. Thus, the

timing of interactions between presynaptic and postsynaptic neurons determines the overall amount of available NMDAr (relieved of Mg⁺⁺ blockage). This is reflected by Hebbian learning rules illustrated through spike-timing-dependent plasticity (STDP). The general takeaway is that neurons that fire together wire together by increasing their mutual coupling strength [105]. The subtlety of this phenomenon has been pruned over time, and whereas the popularization of STDP clarifies how temporal correlation of pre- and postsynaptic firing coincidence directs synaptic strength, it must be understood that this is a simplification of the actual underlying molecular and cellular mechanisms [106,107]. Although this simplification can be a helpful analogy, neglecting the fundamental details obscures the full repertoire of nonlinear dynamics supplanted by synaptic mechanisms. Imprecise truncation of the local nonlinear interactions renders severe alterations in global form and function, as opposed to more comprehensive incorporation of the full repertoire of nonlinear local interactions.

When a postsynaptic cell fires after the presynaptic cell, there are greater numbers of unblocked NMDAr on the postsynaptic site that increase the overall receptor cross-sectional area for this uniquely Ca⁺⁺-permeable receptor. Therefore, if presynaptic neuron firing releases neurotransmitters that diffuse across the synaptic site at the time when NMDAr are unblocked, ligand activation of the NMDAr results in an increased level of Ca⁺⁺ influx. Consequently, intracellular Ca⁺⁺ levels rise, increasing the probability of Ca⁺⁺ secondary messengers activating AMPAr exocytosis. In some situations, different subtypes of AMPAr increase on the membrane that are also permeable to Ca⁺⁺, thereby increasing the probability of elevated Ca⁺⁺ levels [108]. Furthermore, intracellular Ca⁺⁺ concentrations can be modulated by internal release of calcium from intracellular stores. These can be controlled by metabotropic receptor activation [109]. Additionally, multiple types of receptors are expressed, offering a variety of mechanisms across a range of time scales. Of these, ionotropic and metabotropic receptors [110] are some of the most prevalent and widely studied. Ionotropic receptors (or ligand-gated ion channels) typically operate on a shorter time scale, whereas metabotropic (or G-protein-coupled receptors) have longer activation times and work over a longer time-period due to the additional metabolic steps necessary in between agonist binding and elicited postsynaptic response via ion flux. The variety of receptors operating on different time scales further engenders nonlinear interactions amongst constituents. There is a wide multitude of forms of synaptic plasticity used in a variety of brain regions. The objective of this paper is not to provide a comprehensive description of all these forms but simply to provide the general foundations for the various modes of synaptic plasticity in the brain; references [111–114] provide more comprehensive reviews of synaptic plasticity. Figure 1 [115] displays a synaptic diagram with specifications of its relevant components to illustrate how, ultimately, neurotransmitter concentration and cumulative numbers of available receptors influence the magnitude of interactions between neurons in terms of regulating total ionic flux.

2.2. Axonal and Dendritic Structural Plasticity

Axonal and dendritic physiology further provide additional degrees of freedom to modulate connections between neural agents via structural plasticity [116,117]. For example, synapses are housed on dendritic spines, which offer stability to the synapse while supplying it with essential resources to support its activity. Thus, dendritic spine growth must follow synaptic dynamics. Should a synapse be particularly active, dendritic spine growth must increase to support a power-hungry synapse and vice-versa [118]. Dendritic spines provide structural support to synapses and can supply necessary resources which help in facilitate dynamical receptor functions (e.g., modulating receptor expression). Furthermore, dendritic spines help transmit electrical signals to the neuron's cell body, helping process input further. On the presynaptic end, axonal boutons also support presynaptic sites to supply synapses with resources, such as neurotransmitters, thus supporting synaptic strength [119]. Furthermore, dendritic branching [120] offers additional degrees of computation to neurons, increasing the degree of freedom with which neural connectivity

can maneuver. Axons confer additional methods for plasticity on a larger scale [121,122]. The axon is responsible for transmitting an action potential from cell body to axon terminal at its presynaptic sites. Myelin sheaths, produced by oligodendrocytes, are insulating layers encompassing axons made of protein and fatty substances that coat the axon to speed up action potential transmission through saltatory conduction (see Figure 2 [123]). Naturally, the distribution of myelin carries significant implications for the temporal evolution of signal transmission throughout the brain. Axonal arborization can be particularly extensive, connecting a variety of brain regions. Hence, manipulating the signal transmission speed along axonal white matter tracts by controlling the distribution of myelin confers the ability to drastically change firing pattern interactions between relatively larger-scale (with reference to synaptic mechanisms) brain regions [124]. This from of plasticity is highly prevalent to adaptation in the adult brain [125]. Adaptive myelin plasticity modulates the growth and formation of myelin along axon bundles throughout cortical regions to modulate the speed and efficacy of information transfer. In other words, this can change the character of spatiotemporal frequencies of brain activity. High-resolution synaptic connections have been pruned through earlier experiences, restricting how flexible conformation changes can occur at this level. However, adaptive myelination is a form the adult brain commonly uses to refine signal transmission, albeit at a lower spatiotemporal resolution. This explains how young children, with fresh synapses, can learn new concepts to such a high level of resolution. Adults are still capable of learning through adaptive myelination; however, due to synaptic pruning in their youth, the resolution of detail that they can learn is not as refined. For example, an adult can learn a new language; however, it will be far more difficult to learn and achieve the subtleties of a native language speaker's accent.



Figure 1. A simplified illustration of the synapse. Magnitude of interaction is determined by concentration of neurotransmitters and cumulative availability of receptors. Direction of interactions (excitatory or inhibitory) is typically controlled by the type of neurotransmitter released. Thus, factors that influence these parameters control synaptic strength. As synapses are housed on axonal and dendritic structures, their properties also have significant influence on synaptic strength. Reproduced with permission [115].



Figure 2. Myelin sheath distribution by oligodendrocytes on axons to speed up action potential conduction. Adaptive myelination, by controlling distribution of myelin, confers larger-scale modulation of signal transmission dynamics, as opposed to synaptic plasticity mechanisms. Activity-dependent control of myelin distribution along white matter tracts of the brain (connecting different regions) temporally modulates signal transmission, resulting in reconfiguration of connections between larger-scale brain regions. Reproduced from Shutterstock [123].

The direction of such interactions is typically determined by the type of neurotransmitter used. For example, glutamate is used in excitatory neurotransmission, whereas GABA is used in inhibitory interactions. Furthermore, neurotransmitters can elicit modulatory responses. These can entail a combination of excitatory and inhibitory action [124–127] by being able to release multiple neurotransmitter types.

It must be noted that the preceding mechanisms are only the tip of the iceberg, providing a fundamental foundation to describe the various levels of intricate, detailed manipulation in neural connections fueling the emergence of complex brain dynamics. For a more comprehensive review where this subject matter is the main focus, the literature referenced above is recommended. In the context of this paper, it is important to recognize that the variety of biological connectivity entails a wide range of capabilities in precisely fine tuning the nature of nonlinear dynamic interactions across the dynamical hierarchy of the brain.

Furthermore, previous studies have established a preliminary qualitative understanding regarding the underlying biological machinery of the brain. However, to develop further refined insights, these qualitative biological interactions must be quantitatively expressed to precisely encapsulate the inherent nonlinearity and coupling. This can enable further progress by addressing current limitations. For example, current methods lack the resolution and quantitative precision of enumerating global brain dynamics. A theoretical, numerical model describing coupling at the level of synapses can aid in providing a more precise quantitative description. As these global properties are a result of the nonlinear couplings between constituents, defining the degree of coupling can aid in producing refined models and, consequently, a deeper understanding of the brain.

2.3. Quantifying Dynamical Local Coupling

Coupling strength, or interaction magnitude, at the synapse is determined by a combination of highly nonlinear processes, such as (1) the concentration of neurotransmitters in the synaptic cleft and (2) the total number and availability of receptors on the postsynaptic site. Neurotransmitter binding upon receptors is not deterministic but inherently stochastic. Therefore, the concentration of neurotransmitters in the synaptic cleft and the total number of available receptor binding points on the postsynaptic membrane can be used to generate a probability of receptor activation. The probability of receptor activation can be expressed in terms of the total cross-sectional area of receptors that allow for the influx of ions. Using fundamental diffusion principles formulated through Fick's laws, the flux of ions can be quantified with regard to the established electrochemical gradient between the intra- and extracellular space. Thus, the flux of ions multiplied by the total cross-sectional area of receptors corresponds to the total amount of ion influx across the membrane. Incorporating this value with the electrochemical gradient, temporal iteration

$$V_i(t+1) = V_i(t) + \sum_{s}^{S} \sum_{ion} \frac{\nabla \mu * \alpha * J_{flux} * \Delta t}{q_{ion}}$$
(1)

It must be recognized that the electrochemical gradient and flux due to diffusion are relatively stationary. Hence, the term that represents the dynamical nature of coupling is α . This term is fundamentally nonlinear, as it is equal to the total cross-sectional area of the open ligand-gated channels, which is simultaneously dependent on pre- and postsynaptic mechanisms, such as the concentration of neurotransmitters which probabilistically bind upon postsynaptic receptors that may or may not have a voltage-dependent Mg⁺⁺ blockage. Hence, as a product of the variety of plasticity mechanisms, α is stochastic and highly nonlinear. It can influence (1) the concentration of neurotransmitters and (2) the number and availability of receptors on the postsynaptic site. It must be noted that this equation is a foundational factor in quantifying coupling in the brain, particularly on the micro scale. Additional coupling terms, such as adaptive myelination, must be incorporated to comprehensively account for coupling on a larger scale. Furthermore, additional revisions are required to explicitly incorporate and quantify the various biological mechanisms that modulate the dynamical trajectories of neural postsynaptic potentials. Regardless, quantifying coupling at the microscopic scale is a necessary first step towards a more complete model. Nonetheless, the underlying philosophy of this equation can be utilized to aid in quantifying complex local voltage fluctuations due to interactions amongst neuronal constituents.

time and charge for corresponding ion species summed over all synaptic points can represent the voltage fluctuations of a neuron over time. Equation (1) provides a preliminary governing dynamical equation to quantify coupling in terms of postsynaptic potentials. This can serve as foundational coupling law to determine whether a neuron will fire or not based on its synaptic inputs. Voltage (V_i), the energy per unit charge at the next time step, is equal to the voltage at the previous time step plus the summed (over all synapses and ion species respectively) product of the electrochemical gradient ($\nabla \mu$) in joules per mol; the total cross-sectional area of the open ligand-gated channel (α); the flux of ions per area per unit time, J_{flux} ; and the charge per ion species, q_{ion} . This coupling law defines the

dynamical voltage fluctuations of a neuron with reference to its synaptic inputs.

2.4. Local Interaction-Induced Global Characteristics

As described, there is a broad distribution of plasticity mechanisms influencing functional, structural, temporal, and spatial behavior of neural interactions from the micro to macro scale. Furthermore, these mechanisms are not implemented in isolation but incorporated simultaneously, enabling different degrees of maneuverability in connection strength and direction. Consequently, these local interactions are highly nonlinear [128]. When combining these various components, global network dynamics are consequently nonlinear and, when undergoing complex dynamical evolutions, can display chaotic characteristics [129]. These are necessary for fluid multivariable adaptation, as the environment consists of a variety of nonstationary conditions requiring complex physiological form to not only ensure survival but to optimize conditions of survival (e.g., subcortical motivations, steering the quality of life, and gauging reproduction thresholds). Evolutionary adaptation has encoded a fundamental configuration for neural connectivity within the brain, resulting in its natural hierarchical order from birth. Life experiences over time fine tune neural connectivity with adaptive plasticity mechanisms to mold the adult brain. This refines a neural network's instinctive response to environmental stimuli in attempts to optimize its survival.

From a higher-level perspective, global brain dynamics are the processes that steer the network to adapt within the constraints of nature. These are not static in time but highly time-variant from the micro to macro scale, structured in intricate layers of modular connectivity, allowing for coordinated, efficient, dynamic organization [130–134]. Therefore, unique microstate configurations (the exact individual behaviors of network constituents and the degree coupling between these network nodes produced by physiological configurations) determine the global macrostate emergent forms. Thus, the brain is a highly adaptive network whose characteristics change over time to interact with a nonstationary environment. Adaptation entails changing the global properties of a network system over time in response to varying external input posed by environmental conditions. These macroscopic dynamics exhibit transitions from distinct states of global brain function to ensure stability (i.e., survival) in accordance with external situations. Different environmental scenarios, such as scavenging for resources, such as food and water; reading social communication cues; fight or flight response towards predators; sleep; and abstract conceptual thinking, necessitate a variety of distinct global brain functions created by respective microstate configurations of cumulative local neuron interactions [135]. As previously mentioned, the variety of macroscopic distributions (global brain states) is the result of the microscopic configurations of the ensemble's constituents, i.e., the cumulative behaviors and interactions between neurons mediated through their connections with one another, which regulate neural dynamical activity. Therefore, brain macrostate transitions in the form of adaptations to new environmental stimuli are also facilitated by changing the respective microstate configurations. In other words, this corresponds to changing the biological mechanisms between neurons and glia cells by changing the expression or availability of receptors between neurons or adjusting the concentration of neurotransmitters in the synapse [136]. This is similar to how global phase transitions are facilitated by a change in the interactions between molecular constituents [137]. Brain network state transitions are directed by modulating the strength of synaptic and structural couplings between neurons, steering the magnitude and direction of local neuronal interactions that culminate into emergent dynamical trajectories [138]. The governing philosophy of a brain network is that the global level forms and their changes over time are the result of the local-level dynamical interactions of the constituents that compose the ensemble. Hence, the particular microstate configurations in terms of the exact myelin distribution across white matter fiber tracts, dendritic branching, and spine characteristics, along with synaptic efficacy determined by the product of neurotransmitter concentration and receptor availability, cumulatively engender highly nonlinear connectivity. These relationships between network constituents are highly nonlinear and recursively couple upon one another across the temporal and spectral scales of brain activity capable of producing chaotic characteristics.

3. Complex Global Multimodal Synchronization from Local Nonlinear Interactions

The hallmark of a brain network or any dynamically evolving macroscopic system is the ability to orchestrate collective, larger-scale action by coordinating constituent behaviors, generating higher-order levels of influence and stability (as opposed to isolated, uncoordinated individual actions). Interactions between network agents permit coordination of self-organized emergence. Furthermore, the highly nonlinear local properties of interactions allow for stable creation of a wide range of dynamical coupling levels. On the higher-order global levels, this enables flexible creation of a wide repertoire of neuronal circuit types necessary to determine the overall configuration and character of collective, larger-scale network states. Local interactions enable coordination in the form of creating larger-scale forms via gradients of constructive influences (mutually creating a stronger presence together) or destructive influences (interactions that inhibit one another) by controlling the alignment of individual action with reference to each other. For a multiagent network system with the sheer scale and complexity of the brain, ensuring stability or wide-ranging adaptability is directed by fundamental self-organizational principles that promote coordination (in the form of constructive or destructive interactions) amongst individual network components to achieve global network configurations that resonate towards external influences. Accordingly, interactions between multiple agents foster coordination and neuronal collaborations, which set the stage for global dynamical presence (from local collaboration). In other words, interactions between neurons through their various modes of connectivity drive forms of emergence and self-organization. Hence, individual local individual component neural action, through collaboration with other agents, culminates into global brain rhythms and oscillatory activity, which have been recognized and established as hallmarks of brain activity for decades. Therefore, the particular configurations of connectivity across the brain determine how local neural activity interacts to respectively produce unique compositions of overall global network trajectory (quantitatively recognized as nonperiodic behavior [139]. Furthermore, it is known that the cumulative neural interactions compose a brain ensemble's collective global form in terms of neurodynamical oscillations of electrical activity supported by brain physiology. However, a detailed underpinning of how such global behavior is produced through local interactions remains ambiguous. Conventional studies emphasize local configurations, such as small-worldness and modularity, denoting respectively short average path length with high local connectivity and modularity describing dense intrinsic connectivity within a module, with sparse, weaker connections between multiple modules [133,140]. The idea that rich-club hubs (heavily connected nodes) promote global communication among modules has also been proposed, identifying a similar organization in a variety of neuronal systems ranging from the C. elegans nematode to the human brain [1,141,142]. Furthermore, this characterization suggests that structural architecture of the brain compromises wiring cost and its necessary computational ability [1]. Additionally, a hierarchical organization promotes the effective and efficient function of such structures. Thus, past methods have identified the stationary emerged global form using small-world and high modularity descriptions, with scholars hypothesizing as to why such emergence occurs [4,5]. However, this still does not explicitly identify how such complex global organization emerges in the brain. Furthermore, it does not comprehensively define the dynamical transition between these stationarily defined states. In other words, a fundamental understanding of how complex dynamic collective organization is accomplished through local interactions in the brain is sorely lacking. Furthermore, a small-world and modular structural configuration is not explicitly correlated with the dynamical function of the brain in the previously mentioned literature. Small-worldness is ubiquitous in a variety of networks throughout nature. Simply recognizing this in the brain, therefore, does not elucidate significant unique meaning in neuroscience advancing our comprehension of the brain [143]. What it does imply, however, is that there are fundamental universal laws that govern the nature of complex networks, including the brain. However, a broad assessment of small-worldness does not explicitly convey why such emergence occurs and is necessary to support complex the collective dynamics observed in the brain and complexity in general. Therefore, in the following, section, we aim to provide a more detailed understanding as to how global dynamical brain phenomena fundamentally emerge from local configurations, as well as how this structural form is necessary to maintain stability towards a variety of internal and external scenarios by engendering a variety of complex functional spatiotemporal phenomena, a hallmark of healthy brain activity. This has yet to be clearly identified in the brain and must be fully understood to sustain progress in neuroscience. Understanding synchronization would help to assess the emergence of the broad spectrum of neurodynamical frequencies across scales [144].

3.1. Synchronization

The context of synchronization phenomena provides a backdrop for understanding how such emergent self-organization can occur [145]. Synchronization is a fundamental form of collective organization where local interactions amongst oscillators, biological or otherwise, result in coordinated global behaviors [146,147]. Emergence of this form typically carries a higher level of influence and stability as opposed to the uncoordinated actions of isolated individuals. Characteristics of synchronization amongst a population of oscillators are determined in the brain by the physical connections through which neural cells interact. Thus, plasticity mechanisms that can modulate the magnitude and direction of local network interactions can control the global, self-organized forms of synchronization. Synchronization was first formally observed in the 17th century in the undulatory interactions of pendulums placed within close vicinity of each other [148]. Regardless of asynchronous start times, two pendulum clocks, when placed next to each other mounted on a beam, synchronized their oscillations exactly in phase with each other. Their individual motions were not isolated but coupled to one another via the physical mount they were placed upon. Thus, individual oscillatory motions of each pendulum were transmitted as vibrations through the physical mount, interacting with one another. Through interactions, a dominant, emergent frequency of synchronized physical action was displayed by the oscillators. In this scenario, physical coupling led to the constructive and destructive wave interferences, resulting in an emerged synchronized frequency. Over time, further research was conducted to characterize biological oscillators and how this mutual interaction could be used to produce stronger group collective efforts, increasing probability of survival, as the oscillatory rates amongst a population of coupled nodes is typically normally distributed about a center frequency [149].

Synchronization is ubiquitous in nature, as it allows for the creation of global patterns of coordinated movement at a particular frequency (rate of oscillation over time) [150,151]. Self-organization emerges from the cumulative interactions of numerous constituents. Therefore, synchronization is a type of interaction amongst a population of agents who align their individual behaviors by adapting their coupling strengths to constructively amplify their dynamics as a group. This is an efficient method for creating global organization, as multiple agents' collaboration directed towards a common goal can accomplish a task with more stability and persuasion than uncoordinated individual actions. This constructive interaction creates a stronger collective presence as a group capable of withstanding larger external disruptions and with greater influence to steer overall network dynamics.

Strongly coupled neural cells have a greater level of influence upon each other. They can more significantly sway the inherent probabilistic nature of action potential firing in one another. Such neurons can align their dynamics to amplify the activity of their firing frequency, which has a greater probability of influencing other coupled constituents and their behaviors. With larger numbers of synchronized neural oscillators, the amplified action potential frequency is much more capable of altering the trajectory of the global network, as opposed to isolated, undirected individual neuron activity. Therefore, selforganization in the form of synchronization amongst neural cell bodies is a common pattern observed in oscillators to produce stable dynamics that can have heightened impact on molding global network behaviors or better withstanding external and internal attacks. From these, it is observed that synchronization is one of the most fundamental means of creating global order in multicomponent systems. By adjusting the frequency of individual neural firings by adapting the connectivity between constituents, neurons can effectively shift their frequency timings to align their phases and collaboratively produce higher and more stable levels of influence in a neural network. In the human brain, the active adaptation of coupling strength between neurons is accomplished through synaptic and structural plasticity mechanisms [152].

Furthermore, this mechanism changes the degree of coupling (connection strength) and alters the frequency of synchronization (rate of neuronal firing) by which different forms of information are encoded. Thus, synchronization is a desirable form of organi-

zation to provide order amidst highly nonlinear and potentially chaotic brain phenomena [153,154]. This is an efficient method for creating global organization, and such dynamical phenomena are supported by highly interconnected nodes, resulting in small-world structures. Highly interconnected nodes representing a particular module synchronized about a particular center frequency confer an efficient mode of collective organization, conserving wiring costs. This can explain the dynamical form and function of a structural population or cluster of highly interconnected neural cells. Synchronization can make an explicit local correlation between structural configuration and dynamical function (frequency of neural potential firing) [155]. As synchronization is a foundational building block for creating unified order amongst a population of neural cells, a richer understanding of synchronization can aid in better comprehension of complex phenomena, such as perception and even consciousness [156]. Quantifying synchronization in terms of frequency can aid in attempts to bind different perceptual features processed in the brain with mathematical precision [157,158]. A description follows in the next sections of how synchronization is used as a foundational local element to create further complex global forms in the brain.

3.2. Multimodal Synchronization

Whereas the previous can explain the emergence of a single mode of action capable of being represented by a respective frequency, the brain needs to operate on additional degrees of freedom to meet the variety of environmental needs, necessitating further developed complexity. The external environment is often complex, with multiple variables perturbing a network system at different time scales, requiring the simultaneous processing and activation of different spatiotemporal behaviors. For survival, these diverse conditions necessitate higher ranges of adaptability encompassing diverse temporal and spectral scales. Therefore, whereas synchronization is a fundamental form of collective organization amongst numerous individuals (typically at one or a limited scale), brain complexity necessitates multiple forms of collective organization (across multiple scales) to direct the various modes of information internally encoded in the wealth of evolutionarily gifted underlying motivations in subcortical structures to more recently developed cognitive manipulations housed in the neocortex [159–161]. Synchronization gives insight into how small-scale interactions can produce large-scale behaviors capable of accomplishing specific tasks with a larger persuasion to withstand adversity through environmental disruption to maintain local stability. However, the magnitude and direction of this local influence at any one point in time is limited. Broad-bandwidth adaptation, or stability in a variety of scenarios, is produced through higher degrees of complexity. As the brain is responsible for simultaneously performing multiple tasks and handling internal and external dynamics, multiple modes of synchronization emerge to take appropriate actions across different temporal scales to incur broad-bandwidth stability [162]. Hence, at the cost of more expansive and diverse forms of wiring, brain physiology produces high-modularity structures capable of supporting multiple local modes of synchronization. An illustration of such an architecture is exhibited in Figure 3 [163]. The cumulative interactions of multiple modes of localized synchronous activity are necessary to produce the rich repertoire of the global ensemble of brain activity. Thus, clusters of synchronized populations of neurons are necessary to reliably perform tasks, relay information, or interpret sensory stimulus while withstanding a range of external or internal perturbations [164,165]. Brain nuclei, neuronal assemblies, and circuitry responsible for specialized roles in relaying unique patterns of neural activity with larger levels of collective influence emerged through these fundamental characteristics. Mutual interactions of multiple agents are driven by synchronization to create influential coordination (indicated by higher-power spectral response at a given frequency), which can be directed to initiate or trigger communication between brain regions. Through a simple analysis of EEG or fMRI fluctuations, it is obvious that there is no one dominant global frequency of synchronization. However, there is a diverse distribution of multiple modes of synchronization at nonstationary amplitudes and frequencies interacting with one another to perform the beautiful dynamical evolution observed and experienced in

the brain. Potentiation or depression of neural connections through plasticity mechanisms allows for changing of the amplitude of rhythms in the population of neurons to project their frequency information (AP firing rate) at altered spectral powers [166]. Furthermore, these projections alter the dynamics of larger-scale recipient neural assemblies and can gain enough collective strength to influence other cortical regions by recruiting synchronous neurodynamics. Thus, individual neuron firing can influence the firing patterns of other neurons across scales [167] if met with sufficient excitatory actions.



Figure 3. Simplified representation of synchronized clusters of nodes. Multiple synchronous modes representing different amplified and stable forms of information capable of influencing and being influenced by one another. The nonlinear culmination of such interactions composes the overall ensemble of brain dynamics. Reproduced with permission from Russo et al. [163].

This increases the range of dynamical abilities for the brain, as synchronous populations of neural oscillators project information to excite or inhibit one another, competing for influence in directing global network trajectories. Different modes in certain configurations can represent different forms of information, from generating basic emotions from sleep or hunger to more complex forms in higher-order thoughts. Based on sensory input from the environment, along with internal interactions, a dominant pattern of neural activity emerges corresponding to a selected global network configuration, which corresponds to optimizing network stability. The coalescence of this neural firing mediated by connections (or interactions) between neurons creates such larger-scale brain rhythms commonly seen in global patterns, such as the frequencies of electrical activity in the brain. Naturally morphing this band of frequencies into a variety of possible distributions is difficult; however, certain hallmarks of nonlinearity and chaos enable highly effective and efficient reconfiguration of a neural spectral bandwidth by manipulating chaotic bifurcations towards desirable transient states [168]. Thus, this dynamical flow of information representation as neural action potentials is not arbitrary but highly patterned, with rich underlying order that requires a hierarchical, multimodal form to efficiently coordinate rich dynamical phenomena. Efficient organization of this renders highly effective levels of computation, performance, and precision in multidimensional execution driven by biological wave interference constrained by the subtlety of neural action potentials [169,170].

3.3. Complex Forms of Self-Organization

Self-organization through multimodal synchronization directs this macroscopic ensemble as specialized populations of neurons synchronize to particular frequencies across the scales of the brain, producing global, asynchronous, multimodal neural frequencies (i.e., neurodynamic brain waves) [171,172]. The time-varying frequencies of these populations are modulated through the respectively dynamic interactions of connected constituents. Furthermore, different modes at respective spatiotemporal scales serve to encode dynamical information in terms of time-varying frequencies of brain activity to interpret, react to, and survive in an environment that also contains a variety of spatiotemporal perturbations [173]. These processes interact with one another to produce a bandwidth of neural frequencies (brain waves) that attempt to optimize interactions with external disturbances imposed by the environment. Brain physiology and anatomy facilitate these dynamical characteristics to ensure the flexibility of the neural ensemble to locally synchronize while also being able to globally influence the synchronous firing rate (frequency) of other neural populations through connectivity (e.g., properties of axonal arborization, dendritic branching, and synaptic efficacy) [174,175]. These are necessary to maintain stability amidst external attacks by adjusting the power of different frequency responses to excite or inhibit information via neural signals, resulting in the performance of adaptive behaviors. Certain neural populations are synchronized to corresponding frequencies [176]. The unique interactions of these multicomponent dynamics enable modulation of frequency distribution and amplitude to encode different types of information [177,178]. Environmental interactions generally incorporate a variety of diverse phenomena, necessitating unique forms of information to distinguish certain attributes, i.e., distinguishing different frequencies of light, spatial curvatures, sounds, and moods of thought [179]. Consequently, a unique multimodal distribution of neural frequencies across the spatial and temporal scales quantifies the dynamical form of information representation. The cumulative interference of these spectra throughout the brain results in the overall composition of brain dynamics. The manifestation of previous experiences, current representation, and future trajectories is stochastically embedded within these spatiotemporal spectra [180]. Furthermore, the objective of the brain is to refine its possible instantaneous frequency distributions to optimize its performance in the environment. Thus, the overall goal of the brain is to steer its instantaneous spatiotemporal distribution of frequencies over time to optimize its conditions of survival by adjusting its interaction within the environment. This includes planning for future expectations based on previous experiences. Furthermore, these dynamical characteristics are supported by the evolutionarily fine-tuned microstate configurations of a neural network whose coupling configurations are further pruned by earlier developmental experiences, resulting in a unique physiological structure and thus the distribution of myelin, axonal, and dendritic organizations, along with the synaptic efficacy observed in the hierarchical and functionally specialized regions of the brain. Illustrated in specialized regions of the brain, these enable the coordinated emergence of synchronous populations responsible for unique roles in transmitting certain patterns of neural activity that collaborate in composing the overall behavior of the brain [181].

Thus, the brain can be conceptualized as a complex information processing unit, molding its neural physiology as an analog neural network [182]. Processing information through a medium of intricately coupled local action potential interactions (culminating into complex global trajectories), neural circuitry orchestrates interactions across the hierarchical scales of the brain, which combine individual action into collective group order. The latter is typically seen in overall brain activities and behaviors and can be quantified by multiphase, multiscale structures. In the context of memory, different scales of memory structures (working memories and past historical memories) are embedded across spatial scales (from the micro to the macro) and are dynamically observed at different frequencies (high to low). The range of dynamical frequencies are seen in brain behaviors from circadian rhythms occurring on the scale of days to cellular interactions operating on the scale of milliseconds. To encode different forms of information (from memories, or overall shifts in brain behavior), the pattern of dynamical frequencies orchestrated by the brain must be modified.

These modifications are facilitated through the nonlinear connections between constituents in a network [183,184]. Changing local connections (interactions) and their strength between neurons collectively incurs a shift in the global brain state to a potentially more stable (adaptable) form. Changing the degree of coupling between nodes can alter the spatiotemporal characteristics of information flow by altering neuron synchronization characteristics. In other words, this steers the information content of the brain, directing the trajectory of a neural network. As new signals from the environment change the input into the brain, different neural circuitries are activated to represent the new information and relay this throughout the brain [185]. As mentioned previously, this changes the time-varying properties of neural firing in the brain. Hence, over time, dynamical neural frequencies can establish different synaptic weight distributions across cortical regions [186,187]. On a more general sense, the overall connectivity distribution (controlled by axonal and dendritic structures) can also be manipulated to further refine information representation (via altered neurodynamic spectra). This results in different modes of synchronization and a fundamentally distinct spatiotemporal distribution of neural frequencies. Qualitatively, we feel this fundamentally distinct state as the encoding of memories and experiences by our neural network. Furthermore, these can alter subcortical neural connections, slowly fine-tuning habits and personal preferences over time. The brain's mode of encoding information in the spatiotemporal dimensions of brain behavior involves adapting its frequency response accomplished by modifying the variety of locally synchronized clusters, producing global asynchronous dynamics capable of integrating the variety of information a brain network considers when directing its collective form [188]. There is no static state of the brain. The trajectory of a dynamical brain network is consistently being steered by different frequency components of neural firings (projected by synchronized nuclei) interacting and controlling the distribution of the spectral bandwidth, producing brain behavior.

3.4. Examples Observed in the Brain

In sleep, the cortex inhibits afferent higher-frequency neural activity that is typically routed from the thalamus and activated by other brain regions. This assists the brain to inhibit afferents and the tendency towards falling asleep by reducing the power of higher-frequency neural oscillations and increasing the power of lower-frequency delta rhythms [189]. Transitioning into this spatiotemporal distribution of frequencies results in a global transition towards sleep. Processing and generation of information occurs over time to detect, interpret, and act within the environment [190]. Additionally, these neural frequencies serve to potentiate or inhibit information to excite or depress characteristics that determine global network stability. Therefore, the frequency spectrum of brain rhythms serves to encode and propagate needed temporal brain behavior by processing environmental input and generating a global response.

Hippocampal memory index theory also illustrates how dynamical information exchange via spatiotemporal frequencies can be used to encode information to store memories. Neocortical activity projects and encodes unique connectivity configurations in the hippocampus. These can be stored and served as an index to the pattern of the respective neocortical activity by which higher-order thoughts encode the unique connectivity configuration. Thus, future scenarios can potentially activate this index, which, in turn, activates the corresponding neocortical patterns, resulting in an active retrieval of these memories [191]. This allows the brain to revisit past spatiotemporal distributions of frequencies (i.e., previous memories). Furthermore, due to the considerable manipulation of information by the neocortex, upon revisiting these prior memories, higher cognitive thought can review these situations they performed and potentially administer reappraisal to these memories [192]. Reappraisal is a method of reconfiguring these connections, which can enable an individual to potentially learn from prior memories and better adapt in the future (based on potential previous mistakes). Furthermore, this can reconfigure connectivity throughout the global distribution of the brain between the neocortex and other limbic regions.

Across these regions, hierarchical, modular, and fractal brain organization emerges to facilitate multimodal neural synchronization [193]. Such cytoarchitecture exhibits regions of statistical-self similarity to efficiently support the emergence of multiple modes of synchronous populations seen in repeated clusters of highly interconnected modalities [194,195]. In the cortex, this allows the brain to segregate sensory input into discernable

and useful meaning as different modes at different spatiotemporal frequencies encoding information. Furthermore, a self-similar configuration allows the brain to reuse fundamental architectures and dynamical forms to conserve energy in reproducing a variety of different brain states. This self-similar recursion of neural structures is also identified in the columnar organization of the neocortex, giving rise to higher levels of efficient information manipulation necessary to sustain fluid higher-order thought. Additionally, the entire domain of the brain (spatially and temporally) does not have identical degrees of self-similarity [196]. Different regions can have different degrees or dimensions of fractality necessary to support individual responsibilities. Modular brain hierarchies compose these regions to integrate respective information, forming appropriate brain dynamical responses [197]. This complexity is dynamically apparent in the brain through the emergence of bands of synchronized neural frequencies, each mode processing its respective received information and transmitting it to influence its coupled constituents, which cumulatively manifest into the dynamical structure of the brain. Specialized brain regions with unique roles and responsibilities collaborating with one another emerge from these properties. Each region consists of multiple modalities structured in unique ways to perform distinct roles. These regions communicate with one another to steer the global network evolution. Quantitively, this is represented by the bandwidth of neural frequencies (i.e., the frequency components of global brain rhythms) observed in different spatial regions of the brain. Dynamically, these produce brain waves from the delta, theta, alpha, beta, and gamma ranges, spanning from below 4 Hz to above 30 Hz, highlighting the variation in the spatiotemporal scales of a dynamical complex brain network [198]. Functionally and anatomically distinct brain regions with specialized capacities emerge from these principles. Therefore, multimodal functional integration is typically observed as the interaction of different frequencies (corresponding to the representation of forms of information). Largescale integration producing a dynamical brain state is conducted through the coalescence of different frequencies mutually interacting to produce a bandwidth of neural frequencies at any one point in time. It is noteworthy that to maintain stability, this band of frequency responses must be able to constructively interact with each other and environmental perturbations to optimize the probability of survival. In other words, unique synchronized modalities and systems with distinct roles emerge in a mutually beneficial relationship with each other to nurture a global composition of neural frequencies, which serves to constructively interfere with the disruptions imposed by the environment [199].

Globally, canonical circuits are recursively exercised to facilitate the flow of synchronous and asynchronous neural activity at different frequencies to compose ensemble brain cell dynamics. A modular organization facilitates the formation of different modes of synchronization [200]. These smaller units (modules) are where similar neural circuitry is iteratively repeated, forming a columnar organization, allowing for basis multimodal synchronous activity throughout modules enabling effective information transfer across scales [201]. Different modules (at different synchronized frequencies) can interact with one another to influence dynamical characteristics, thereby further processing information across scales. A structure of this nature allows for segregation or integration of complex, multi-scaled information, as previously mentioned. This fundamental cytoarchitecture is implemented from the micro to macro scales of the brain. That is, nuclei of brain regions and larger-scale structures serve unique roles and collaborate with one another through their interactions to produce a global dynamical brain state similar to how microscale columnar modules produce multiple modes of synchronous neural activity and interact with one another to process information. Thus, statistical self-similarity is exhibited across scales of the brain [202]. Spatially, this is observed in modular organization of neural populations, resulting in larger-scale brain nuclei and consequently producing different brain regions with respective degrees of statistical self-similarity. For example, the most recently evolutionarily developed part of the brain, the neocortex, is responsible for higher cognitive thought [203]. This largest part of the cerebral cortex is organized into multiple layers of interconnected neural populations to facilitate efficient information transfer necessary to

drive flexible conscious thought [204]. This region will have a different fractal dimension than the following. The different lobes of the cortex are responsible for processing different types of information (sensory input, such as sight or touch, and sending out physical action output). Each type of sensory input is inherently composed of multiple components. Consequently, multicomponent inputs are segregated by cortical structure to discern valuable meaning with reference to what the brain already knows. After relevant information is extracted and understood by the brain, this dynamical organization of the cortex integrates this information with meaning attached to it to formulate an appropriate collective response. The brain interprets this information as a unique distribution of neural firing frequencies over time to understand the environment. Sensory input, in the form of a unique pattern of activity, interacts with cortical structures, eliciting a unique response by interacting with and then activating a unique pattern of neural firing frequencies. Unique synaptic weights (or microstate coupling configurations) create this macroscopic distribution of frequencies. As previously mentioned, these different forms of information are encoded via multiple modes of synchronized neural frequencies [205,206]. Different frequencies bifurcate to segregate information and contrastingly coalesce to integrate information. Thus, the organization of cortical physiology is responsible for accomplishing these tasks and interpreting and transmitting information. This distinct spatial organization created by layers of highly interconnected neurons facilitates the generation of synchronized neural firings amongst highly coupled clusters and fosters the interplay of multiple modes of synchronized neural clusters generating complex spatiotemporal neurodynamics [207]. Furthermore, these neocortical dynamics are also influenced by subcortical activities. The neocortex receives sensory information routed from the thalamus [208,209]. These excitatory projections encode specific forms of information in signal attributes, such as the frequencies of action potential excitations. Upon this, a preliminary assessment of sensory input is generated. Consequently, the cortex can send projections back to the thalamus to process higher-order cognitive manipulation, which allows different layers of cortical connectivity to process information together. Furthermore, through the thalamus, the neocortex can send or receive information to and from subcortical structures (e.g., limbic regions, such as the amygdala) through higher-order relays to influence underlying motivation, emotion, bias, and perception [210,211]. Thus, thalamocortical and corticothalamic loops represent one example of how different regions of the brain collaborate with one another [212]. Importantly, the basis for information transmission by these regions is synchronized neural action potential activities. Additionally, these processes are modulated through the degree of coupling between constituents, by which the spectral power of neural activity is controlled across spatiotemporal scales over time. Therefore, structural and synaptic plasticity mechanisms excite (or depress) connectivity, propagating (or inhibiting) frequencies of synchronized populations recursively across the modular spatiotemporal organization of the brain. The interplay of these mechanisms allow for potentiating or inhibiting certain behaviors. These collectively produce (and adapt if need be) the multimodal dynamical ensemble of the brain. In other words, neural physiology is responsible for simultaneously providing stability to neural brain dynamics and degrees of plasticity when global dynamics must change or refine its organization [213,214].

Perhaps one of the most frequently observed brain characteristics representing how different regions of the brain communicate and interact with each other is neuronal ensemble oscillations (resulting from neural AP interactions), producing the vast degree of complexity in neurodynamical phenomena [215]. The temporal correlation of activity across these brain regions (from the micro to macro scale) determines how strongly certain functional configurations are reinforced from the possible range of configurations produced by physiological structure. Multimodal synchronization allows for the complex algorithmic manipulation of information by creating centralized regions responsible for unique roles. For example, neuromodulator systems work in concert with one another to direct higher cognitive thought in prefrontal cortex activity [216]. These incorporate noradrenergic, dopaminergic, serotonergic, and cholinergic systems influencing each other

while projecting and receiving signals to their respective targets. Having multiple systems responsible for specialized roles and coordinating their action amongst gives higher degrees of freedom for a system to encode information into meaning to perform a task. Together, these shape prefrontal cortex activity, which consists of a variety of subregions that send and receive information (via the thalamus) to and from other subcortical structures, from motor and sensory systems to memory and motivational state processing sites [217]. The magnitude, direction, and rate of these global spectral signals are manifestations of local constituent interactions.

The brain incorporates multiple mechanisms in performing a variety of tasks and effectively changing these tasks in accordance with its environment. These include initial appraisal of sensory input, discerning meaning from processing this information, and planning future action (or thought) based on the understood meanings. For example, as an individual is reading and taking in sensory input, the brain is simultaneously transforming the images of words into semantic meaning and cross referencing this information with previously known conceptions and new innovative ideas. (It is noted that this does not consider the simultaneous regulation of basic physiological processes, such as heart rate and circadian rhythms, to more complex refining of subcortical motivations and primal instincts.) Clearly, the brain's complexity serves a necessary purpose of performing a variety of tasks briefly elucidated above. This enables integration of the vast amount of information present in the brain encoding personal experience, as well as previously embedded evolutionary adaptation constituting inherent predisposition to formulate a coherent system response encrypted and administered through the characteristics of spatiotemporal dynamical neural firing [218]. Sensory input is translated into meaning via a unique pattern of neural firing. The neurodynamic rhythms influence and interact with other brain regions, eliciting a sufficient response.

Furthermore, the structural network configuration produced by brain physiology must be functionally degenerate [219]. In other words, particular structural configurations must be capable of supporting a wide repertoire of functional dynamics to support brain function with respect to various environmental scenarios. These are supported by intricate structural configurations fine-tuned through developmental and experiential plasticity. Studies have identified this structural–functional degeneracy [220]; however, a clear explanation of how a single functional dynamical global state is selected out of the many possible states is lacking, and why this structural–functional degeneracy is necessary for the brain to reconfigure and adapt rapidly is unclear.

3.5. Defining the Brain Quantitatively

A global state of the brain can be described in terms of the emergent oscillations of neural activity [221]. This system is consistently perturbed by internal and external stimuli. Internal stimuli can be patterns of local activity that interact with critical regions, gain influence, and threaten to sway the overall neural network trajectory for better or worse. This can be qualitatively observed as an individual thought that inspires significant change or, in pathological conditions (e.g., hallucinations, schizophrenia) where internal disruptions are not properly mitigated, may lead to network collapse [222,223]. External stimuli are typically in the form of sensory input. Processing of a variety of sensory information is accomplished by encoding raw sensory stimuli as unique patterns of neural activity that can trigger unique distributions in global neural activity [224]. This quantitative form encodes understanding, behaviors, and reactions in the global network. For example, sensory systems are hierarchically organized to extract relevant multicomponent information. Hierarchical organization is conducive to facilitating interactions between multiple frequencies of neural activity and is thus capable of efficiently harboring, processing, and morphing spatiotemporal spectra of activity across scales [225]. Sensory input, once converted into patterned electrical activity, thus activates unique compositions of the spatiotemporal spectra activity, encoding unique sensory information. Consequently, different types of sensory information are expressed as different spatiotemporal patterns of

neural activity. These inherent variations, small differences in initial conditions of different types of sensory information, can elicit dramatic deviations in the processed results. Identification of an environmental scenario is represented by a particular pattern of activity, which is a construct of multimodal synchronous neural populations [226]. This composition of frequencies and various amplitudes (conveying sensory information) interacts with the activity of other brain regions (which are also producing a unique composition of neural frequencies and amplitudes). The consequent quasi-biological wave interference produces an emergent neurodynamical form of activity corresponding to reaction towards sensory input. In reaction to a threat in the environment, this can produce spatiotemporal neural activity correlated with a fight-or-flight response. Small variations in initial sensory input and internal motivations, once processed throughout the cortical structure, result in the possible emergence of a variety of functional states corresponding to a possible fight-or-flight reaction. This selection of functional states occurs for a variety of scenarios, from simply deciding what foods to eat to determining a response in a social scenario. Additionally, the possible selected states may be chosen based on free-energy minimization principles to optimize network efficiency by conserving precious energy and maximizing productivity [227]. Furthermore, brain network structure degeneracy is limited [228]. Only a finite number of functional states can be represented (due to energy limitations); however, fine tuning of structural physiologies through plasticity mechanisms can enable the brain to refine its possible functional states and learn new configurations. Encoding new configurations (via plasticity mechanisms) occurs at a cost; however, utilizing a hierarchical structure can maximize the number of functional states that can emerge from a selected coupling configuration throughout a neural network. Naturally, selecting which structural configurations are necessary is dependent upon which functional states efficiently optimize an individual's survival. It is noteworthy that this reaction is almost instantaneous, as an instinctual response is orchestrated upon immediate detection of sensory stimuli. Thus, this is a highly efficient way to rapidly produce a global system response immediately upon interacting (or interfering) with the environment. Due to the resolution limitations of biological figures such as the brain, the response is not instantaneous, as there is always an inherent temporal lag in the brain network processing, interpreting, and reacting to the environment. Despite this, global system response occurs on the scale of milliseconds.

Thus, brain physiology refines its form through neuroplasticity to better adapt its degenerate functional dynamical forms, that is, its instantaneous spatiotemporal distribution of frequencies. For example, the particular configuration of connectivity in evolutionarily older brain systems, such as the limbic regions, quantitatively provides different patterns of neural activity, which are qualitatively felt as aspects of emotional processing capable of projecting influential information upon the cerebral cortex and swaying the higher-order processing of emotion [229,230]. Complex forms of information manipulation accomplished by the neocortex allow for review of such fundamental raw emotions to better reconfigure towards a logical assessment should this lead to more optimal survival conditions. Orchestrating a complete physical reaction takes less than a second [231]. Purely cognitive reactions (mentally recognizing an environmental scenario) can take even less time.

Such agglomerations of different forms of neural activity mutually interact with each other to manipulate the flow of information in an attempt to direct a beneficial collective ensemble response. This entails creating a network structure which is capable of higher degrees of adaptation (in accordance with unique environmental situations) to better optimize all the opportunities external conditions may pose. Qualitatively, this can be thought of as the different aspects of consideration an individual recognizes when deciding what action or route to take. The harmony of these multimodal processes is essential to efficiently direct the trajectory of the ensemble towards obtaining dynamic stability in time with respect to the dynamical environment. In other words, these specialized modes of synchronization do not work in isolation but co-operate with each other with specialized roles to process and relay relevant information throughout the brain. Cross-modal reliance causes the distribution of synchronized frequencies to be highly sensitive to external and internal influences and changes [232]. For example, a slight variation in information transfer in one cortical area (new sensory stimulus) modifies the interactions with other cortical and subcortical regions. Thus, through cross-modal reliance, new information being transmitted by a particular modality can have a cascading, rippling effect across the spatiotemporal scales of a network, which influences the reorganization of the macroscopic ensemble's frequency response, resulting in a global configuration towards a (in healthy brain function) desirable state [233].

Multimodal synchronization, observed as multiple frequencies of neural clusters mutually interacting, results in highly complex and nonlinear behaviors [234,235]. Scenarios ranging from chimera states to neuronal avalanches to explosive higher-order simultaneous synchronous and asynchronous states in dynamical networks are highly critical states that stem from different spatiotemporal scales of synchronization present in the brain [236,237]. The criticality of these states (stemming from the inherent nonlinear nature of the brain) is necessary to enable effective adaptation by changing the distribution of multimodal activity to better adapt to new deviations in a situation that necessitates a different form of emergent brain dynamics to maintain stability [238]. In critical states, certain perturbations or influences can bifurcate frequency responses and trigger neuronal avalanches [239,240]. In pathologies, these are not regulated and can rapidly deteriorate the state of the brain. However, in normal cognitive function, this is directed to produce a new brain state that is adaptable to the new environmental disturbances. Therefore, environmental input not resonating with the current state of the brain can engender network deterioration due to highly nonlinear and critically dynamic forms breaking down the previous functional states, allowing for new functional states to take place. If directed properly, transitions can be facilitated effectively to rapidly adapt brain form and function to create desirable configurations. Fight-or-flight response, high-pressure social communication, or simply waking up from a deep sleep in response to a loud noise are examples of global transitions that are highly nonlinear and effectively directed in most healthy brain networks [241]. There do exist certain pathologies that compromise the biological mechanisms of brain function preventing the effective facilitation of these dynamical transitions [242].

Thus, the local degree of couplings between neurons controls global brain dynamics by changing the interactions between neural firings resulting in potentiating or depressing information. Increasing the degree of coupling (stronger connection) can reinforce particular patterns of neural frequencies to result in an increase in the influence of the corresponding spectral response in the global bandwidth of neural frequencies. Contrastingly, neural firings can also diminish the influence of certain spectral responses by depressing certain connectivities. The emergence of these types is mediated by different degrees of coupling (interactions) to project or inhibit information based on whether it is desirable for the survival of the collective. Thus, broadband collaboration between constituents is the fundamental basis for complex behaviors commonly seen in the interplay of neural frequencies throughout the time evolution of a network ensemble. Neurons coordinate their individual actions with one another through their interactions to produce macroscopic oscillations across the spatiotemporal scales of the human brain. Based on assessment of the produced macroscopic interactions with the environment (in the form of how successful the brains distribution of neural activity is in accomplishing a task), neuroplasticity mechanisms can alter couplings to further refine the global distribution of neural activity if necessary (if performance improvement or change is needed).

Hence, a bandwidth of neural frequencies (quantifying the dynamical state of the brain) is simply the interaction of multiple synchronous clusters representing different components of information across the scales of the brain. The combined collaboration and competition amongst these dynamics produce the emergent dynamical features of the brain. Time-varying properties that dictate the trajectory of a neural network's behaviors are determined by the microstate configurations of connectivity (degree of neuronal coupling distribution). The exact character of synapses, dendrites, axonal architectures, and myelin distribution, along with other physiological factors controlling coupling in a brain network,

determine how individual components, from single cells to clusters and regions of the brain, interact with one another to manifest the overall dynamical form of the brain. An emerged frequency distribution of the brain, produced by its cumulative subordinate interactions, serves to interact with the external environment. Resulting environmental interactions are processed by the brain to assess its own performance and administer changes if needed to better manipulate its dynamical repertoire for seizing opportunities posed by the environment. Environmental opportunities may change at a moment's notice, necessitating the brain to shift its frequency distribution (spatiotemporal spectra of neural action potentials). Consequently, changing the bandwidth instills degrees of nonlinearity, including route-to-chaos [243]—both are dynamical evolution characterized by bifurcation of spectral response. Relationships between network constituents are highly nonlinear and recursively couple upon one another across the temporal and spectral scales of brain activity, capable of producing chaotic characteristics. Despite experiencing dynamic instability to different degrees, the brain is remarkably adaptable to finding stability. Therefore, uncovering the fundamental nature of how the brain maneuvers its "route to chaos" can be applied to a plethora of real-world systems that exhibit nonlinear and chaotic characteristics. Instability is typically characterized by unprecedented levels of change in the system. Typically, such a high degree of changes is viewed as undesirable, as bifurcation increases the probability of system instability. However, if instability is controlled, the degrees of changes can facilitate highly efficient reorganization towards a desirable state. The brain manipulates its high degrees of nonlinearity in its favor. From a plasticity point of view, these can enable the brain to rapidly reconfigure and adapt to new scenarios more effectively than a highly statically stable network system with strongly reinforced configurations (as it may be more difficult to break out of these prior conventions and adapt to a new global state). Therefore, characteristics of instability exhibited by bifurcation of dynamics represented in the brain through the criticality of neural activity are manipulated by the brain to enable its proficient ability to adapt. This is further exhibited by the various modes of functional forms a neural network can assume from a fundamental physiological structure capable of performing a wide range of activities. Neural bifurcations are effectively directed towards rapidly reconfiguring the spatiotemporal distribution of frequencies in the brain toward a state that is better able to adapt in the environment. The number of possible network configurations is very large, to say the least. However, the brain isolates, refining a finite number of network configurations using a canonical, self-similar pattern and structure across its temporal and spatial scales. This directly corresponds to the statistically self-similar fractal nature of the brain. In qualitative terms, this directly correlates with the unique style, personality, or character of a brain network in terms of having a fundamental go-to protocol, method or philosophical way of thought (unique pattern of neural activity), which is administered recursively upon the variety of scenarios the environment poses. Self-similarity across the multivariate scales of the brain is therefore essential in supporting efficient dynamical transitions by directing chaotic bifurcations in its own hierarchical structure to effectively filter information throughout the scales of the brain while conserving resources through a self-similar organization [244,245].

4. Concluding Remarks

The aforementioned information serves as a general overview of our understanding of how brain form and function changes over time within the constraints of nature. This review is by no means complete. For example, the exact form of emerged spatiotemporal brain dynamics is unknown. According to literature reviews, brain structure and physiology enlist small-world structures to create multiple modalities of highly connected populations internally synchronizing and externally interacting with other populations in aperiodic characteristics. Hence, this biological structure engenders fundamental dynamical building blocks of synchronized neural populations. When these pieces are put together from the micro to the macro scales of the brain in unique configurations (gifted by evolutionary fine tuning) and molded by developmental and experiential plasticity, simple local activity can coordinate complex higher-order global forms, directing the trajectory of a brain network. Structurally observed in high-degree modularity, functionally, this enables the interaction of multiple modes of synchronized clusters. Local fundamental building blocks center around respective single-frequency components interacting with one another to create complex spectral distributions (multiple-frequency components). This spectral distribution inherently changes over time to support survival needs. Different regions of the brain have different connectivity configurations, enabling production of unique patterns of neural activity. Consequently, the amalgamation of these structures from the most fundamental constituent to the global level of the brain produces a unique spatiotemporal spectral distribution with an aperiodic trajectory that encodes information in the brain, incorporating abilities to (1) acquire and process sensory input and (2) initiate response (not necessarily physical). Quantitatively, this can be represented in terms of the spatiotemporal distribution of neural action potential frequencies, where the evolution of this distribution over time encapsulates the dynamical state of the brain. Therefore, brain dynamics (experienced and observed) can be concisely, consistently, and precisely defined as how this functional spatiotemporal distribution of neural activity morphs over time with the support of fundamental neural biological mechanisms. Global neural activity is not random but highly ordered and supported by hierarchical structures. This form is recursively implemented from the micro to the macro scale and allows the brain to effectively produce complex forms of information representation (by composing unique spatiotemporal trajectories of neural dynamics), enabling performance of a wide range of activities while efficiently consuming precious resources necessary to sustain such dynamics. Furthermore, these forms entail self-similarity to optimize energy consumption in balancing and keeping certain network attributes similar (minimizing energy expenditure) while being required to change other network attributes (to adapt in the environment). Hence, a potential solution towards addressing neurodegenerative diseases and implementing brain-machine interfaces is to administer active control upon a neural network's spatiotemporal distribution of frequencies. Moving towards a more general step, effectively administering control of the complexity present in the brain can also provide insights towards the nature of complexity in our universe.

Due to our lack of understanding of the nature of brain dynamics and resolution limitations of current approaches, the precise form of the brain's spatiotemporal distribution of activity has yet to be comprehensively defined or modeled. The precise understanding of the following remains unclear: (1) what is the exact temporal evolution of neural activity in one region of the brain (for example, the thalamus routing information from the amygdala) and (2) how this interacts with the temporal activity of another region of the brain (the neocortex), producing emergent neurodynamic frequencies qualitatively observed or experienced as processing and acting upon fearful stimuli elicited from the amygdala. It is known that these are produced through the fundamental coalescence of individual neural activity coupled nonlinearly upon one another. However, to attain an improved understanding of brain dynamical phenomena and potentially administer active control, a more precise definition is necessary. Specifically, this means being able to (1) mathematically represent a spatiotemporal spectral distribution of neural activity and (2) establish a governing dynamical law that can describe how such distribution changes over time. Mathematical representation ensures precision and entwining this with fundamental physical laws governing dynamical interactions ensures the creation of a comprehensive model that can comprehensively encapsulate complexity in the brain. A more precise interpretation not only renders higher levels of comprehension towards the subtleties behind spatiotemporal spectral distribution of neural activity but can also enable active control of such phenomena towards more desirable trajectories.

Years of evolutionary fine tuning have trained the brain to manipulate the laws of nature represented within its physiological form. This process entails a wide variety of disciplines, rendering any single perspective inadequate and insufficient to analyze the brain. A transdisciplinary approach is required—one that allows the fundamental laws of physics to be entwined within brain biology to comprehensively illustrate the dynamical ensemble of the brain.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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