Puzzling challenges in contemporary neuroscience: Insights from complexity and emergence in epileptogenic circuits

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ABSTRACT

The brain is a complex system that, in the normal condition, has emergent properties like those associated with activity-dependent plasticity in learning and memory, and in pathological situations, manifests abnormal long-term phenomena like the epilepsies. Data from our laboratory and from the literature were classified qualitatively as sources of complexity and emergent properties from behavior to electrophysiological, cellular, molecular, and computational levels. We used such models as brainstem-dependent acute audiogenic seizures and forebrain-dependent kindled audiogenic seizures. Additionally we used chemical or electrical experimental models of temporal lobe epilepsy that induce status epilepticus with behavioral, anatomical, and molecular sequelae such as spontaneous recurrent seizures and long-term plastic changes. Current computational neuroscience tools will help the interpretation, storage, and sharing of the exponential growth of information derived from those studies. These strategies are considered solutions to deal with the complexity of brain pathologies such as the epilepsies.

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1. Looking for a change in paradigm in contemporary neuroscience

On the occasions we talk about “dogmas” in science we refer to those persistent views that are long-lived despite repeated demonstrations against them. It is our view that in more recent decades, one excellent example of these famous dogmas in neuroscience is the affirmation that neurogenesis is not possible in adult brains. Despite the original demonstration of its occurrence in adult animals [1,2], the fall of this dogma was possible only decades later, after a multitude of confirmative studies and even with the demonstration of its existence in the human brain by Fred Gage’s group at the Salk Institute [3]. In my view, one of the best historical reviews of that conflicting interpretation and the consistent negation of its existence was that by Gross [4]: “In the first half of the twentieth century, there were occasional reports of postnatal neurogenesis in mammals but these were usually ignored by textbooks and rarely cited.” He then continues: “Presumably this was because of the weight of authority opposed to the idea and the inadequacy of the available methods both for detecting cell division and for determining whether the apparently new cells were glia or neurons.” Obviously, to dispel a well-preserved dogma such as this and, despite a previous description of the critical phenomenon that denies it, experimental replications are needed because it is necessary to certify, first, whether variations in the technicalities can be associated with the difficulties in reproducing the data. In the case of neurogenesis, initial questions were related, for example, to the difficulties in differentiating small neurons from proliferating glia. But, as stated by Gross [4], although Altman published in prestigious journals such as the Journal of Comparative Neurology, Science, and Nature, these findings were totally ignored for decades, and even after the studies by Kaplan [5] that were confirmatory of Altman’s data and further demonstrations by Burd and Nottebohm [6] of neurogenesis in birds, the dogma was not changed.

Fortunately a huge number of confirmatory experiments came later, some of them related to new developments such as bromodeoxyuridine and specific neuronal markers (MAP2, Ki-67, NeuN), which sealed the confirmation of the existence of neurogenesis as another important phenomenon in brain function. Still, there is currently a growing number of experiments searching for the actual role of neurogenesis in ontogenesis, learning and memory, cognitive function, neurodegeneration, and neuroregeneration [4,7,8].

Other stories in neuroscience research are probably not as dramatic as that of neurogenesis, but in your daily research, have you ever been confronted with paradoxical observations and eventually tried to replicate literature data without success? Also, have...
you tried to answer, with specific protocols, unanswered neurobiological questions, but at the end of those experiments, and with a lot of data in hand, you feel that there is always something that is lacking and urgently needs to be done? We know that when coupling the idea that generates the experiment with the technical resources used to test its viability, you can end up with either clear-cut, linear, ambiguous, or complicated answers or, in the worst situation, no answers at all. If a given technological development is used with animals and eventually in humans, will this kind of protocol produce linear, ambiguous, inconsistent, complete, or incomplete answers? Are conflicting observations or interpretations always signs of wrongly designed experiments, strain differences, or subtle protocol changes?

It might be that none of these explanatory conjectures is correct, but simply that we are dealing with several causes of biological variability inside what is fallaciously considered the same system, but is evaluated differently from the point of view of a variety of strategies. What about when we try to compose the whole neuron–brain picture, taking reductionistic, so-called well-controlled approaches and, in rare cases, coupling these to other levels of analysis such as neural circuits and even behavior? Has the latter consideration something to do with the scientific method at the level developed in Western science? How much of this is simply the consequence of a lack of transdisciplinary approaches, and in the best situation, if that approach has been used, is it a consequence of the difficulties encountered in putting things together and coherently?

A very clever example of the concept of transdisciplinary thinking comes from the studies of Albrecht et al. [9] on complexity and human health. These authors state that transdisciplinary research enables researchers to pursue the interplay across disciplines and theories in constructing multilevel explanations anticipating emergence of a common conceptual framework capable of unifying these multiple explanations. Complexity theory is considered a potentially powerful unifying construct for understanding the nature of complex, dynamic systems, and in their case, health problems.

After this avalanche of questions, my main goal in this review is to propose that instead of continuing to collect and analyze neurobiology data at separate levels, from behavior to circuits to cells and molecules, and eventually at unconnected multilevels, we need urgently to agree, first, that the systems we are dealing with in neuroscience research are complex. This is not exactly a new concept in the neuroscience field, but simply one that has been neglected over time. Second, after agreeing on the definition of the brain as a complex system, we need to accept it is a system capable of having emergent properties expressed differentially in normality, such as activity-dependent plasticity typical of learning and memory, and in pathology, such as the lesion-associated plasticity of neurological or even neuropsychiatric disorders.

I thus encourage discussions on new ways to conduct contemporary neuroscience research. Some examples in support of this proposal are derived from my own experience with epileptology studies over the last two and a half decades. At the end, I discuss briefly current concepts, strategies, and methodologies, already in use worldwide, that I believe are fundamental to my view and propose future avenues of research.

Parts of this review were presented in a recent article [10]; however, in the current article, I go deeper and extend several issues while at the same time touching on new ones.

2. Transdisciplinary neuroscience: Brain complexity and emergence

I begin by pointing to a recent publication from the New York Academy of Sciences, “Tempos in Science and Nature: Structures, Relations, and Complexity” [11], that is illustrative of the concepts of complexity and its associated phenomena.

In the preface to this issue of Annals of the New York Academy of Science, Rossi and Tiezzi [12] call attention to the fact that a change in paradigm is needed for current scientific theories in view of the natural situation of the planet. Along this line, they cited Italo Calvino’s character Palomar, who says: “If the model does not succeed in transforming reality, reality must succeed in transforming the model.” To avoid this paradox, the authors say, “shift to a new interrelated paradigm is necessary: this is a challenge for science in the new millennium.” In the same preface, the authors call also attention to the fact that “complexity is an opportunity for re-uni-fication of the scientific culture and the humanities.” Moreover, and I strongly agree with these authors, “it is important to underline the fact that the complexity of nature has made it necessary to develop concepts and theories that have little in common with the reductionist and mechanical approaches that have dominated scientific thought for two centuries” [12].

The authors complete their preface by emphasizing that to achieve transdisciplinary goals, “it is fundamental to harmonize our scientific knowledge with aesthetics, the humanities, genetic epistemology, and everything else dealing with complexity.” And this statement is in absolute consonance, and we also agree on that, with the concept of consilience discussed in recent years by Edward O. Wilson [13], the father of sociobiology, and strongly echoed in another Annals issue entitled “The Unity of Knowledge” [14]. In the same direction, even more recently, Segerstrale [15] treats Wilson as a convergentist because of his attempt to unify science and knowledge—exact, natural, and human sciences.

Goldenfeld and Kadanoff [16] state that “complexity means structures with variations,” and by the same token, “living forms are complex because of their different working parts, each one formed by variations in the working out of the same genetic coding.” These authors also contrast the simplicity of the basic laws of physics with the laws of the world. They claim that although every foundation of our world view is lawful, and everything is simple and eventually expressible in terms of everyday mathematics, what is not simple is the world! They also ponder that outside the physics classroom, the world is complex in every corner we look: mountains, dunes, waves, financial markets, with the biological systems being what they call “a limiting case of exceptional complexity.” As another “elementary lesson,” Goldenfeld and Kadanoff [16] pose: “nature can produce complex structures even in simple situations, and can obey simple laws even in complex situations.”

Additionally, Ronald [17] discusses emergence in the field of artificial life in the following terms: “The description of a phenomenon as emergent is contingent, then, on the existence of an observer; being a visualization constructed in the mind of the observer, emergence can be described as a concept, like beauty or intelligence.” He points out that to consider a phenomenon as emergent, the element of surprise is also needed, which is a consequence of the non-obviousness caused sometimes by self-organizing phenomena or sensitivity to initial conditions (chaos).

Amaral et al. [18] call attention to the increasing focus on so-called disordered networks because of their potential as models for the interaction networks of complex systems. They talk specifically about small-world networks. The best examples of this kind of network are social networks, for example, close friends who cluster through social contacts. However, it is possible for a person to have someone located far from home who knows the people closest to him or her. Watts and Strogatz [19] demonstrated that, as in the case of the social networks, without affecting local clustering, the existence of a few long-range connections greatly reduces the minimum path length of the network. The algorithm they produced defined what are called small-world networks.
Briefly, Watts and Strogatz [19] stated that when nodes are connected with their nearest neighbors, a regular graph is produced that has a high clustering coefficient and high average path length. When edges are randomly rewired (with a probability $P$), if $P = 1$, all edges rewrite randomly, which means the resultant network is perfectly random (short average path length and clustering coefficient). However, when $0 < P < 1$, the resultant graph is a small-world network with high clustering and low path length, a combination of some dense local clustering (regular networks) and some long-range connections (random networks).

One consequent question asked by Bassett and Bullmore [20] is: Why should we think about the brain as a small-world network? They review the empirical and theoretical reasons small worlds represent an attractive model for brain network connectivity and also review mathematical methodology and empirical findings in more detail. Summarizing, Bassett and Bullmore [20] list what they propose are the reasons that motivate the study of the brain as following small-world network rules: first, the brain is a complex network on multiple spatial and time scales; second, the brain supports both segregated and distributed information processing seen in sensorimotor and cognitive processing, localized discretely in specialized regions or large-scale distributed systems; third, the brain likely evolved to maximize efficiency and/or minimize the costs of information processing while supporting high dynamical complexity.

What is interesting for the current review is that there is a growing literature suggesting that small-world networks rules fit quite well with brain anatomy [21], brain functional normal circuits [22], and even epilepsy-related phenomena [23]. Some of these approaches are discussed in more detail at the end of this review as they are considered future computational neuroscience solutions.

In the particular case of the nervous system, Koch and Laurent [24] emphasize that even “simpler” nervous systems have extraordinary complexity reflected in their functions, evolutionary history, structure, and coding schemes for information processing. How to address all these features in an integrated manner is one of the more challenging tasks of current neuroscience research. Because classic and modern techniques allow us to perform a vast number of inquiries into each one of those layers of complexity, Koch and Laurent [24] also strongly state: “realistic notions of brain complexity must incorporate, first, the highly nonlinear, non-stationary, and adaptive nature of the neuronal elements themselves and, second, their nonhomogeneous and massive parallel patterns of interconnection whose “weights” can wax and wane across multiple time scales in behaviorally significant ways.”

3. Epileptogenic circuits as sources of complexity and epilepsies as their emergent properties

One recent example of the use of the concepts of complex systems and their emergent properties is taken from the studies of Faingold [25], who addressed, on the basis of the selected background of genetically epilepsy prone rats, the ability of brain circuits to change after repeated audiogenic seizures, in a timely and organized fashion that allowed observation of those altered structures as targets for new pharmacological anticonvulsants and even antiepileptogenic agents. In a similar direction, although with a completely different model, limbic seizures induced by chemical or electrical stimulation, Sutula and Dudek [26], recently proposed, using a detailed anatomical characterization of the sprouted mossy fiber pathway in the dentate gyrus of the hippocampus, that a great majority of sprouted synapses in the inner molecular layer of the dentate gyrus form recurrent excitatory connections, which will be more significant contributors to recurrent excitation and potentially to enhanced susceptibility to seizures. This is not exactly the whole story, because some sprouted axons also form synapses with inhibitory interneurons, which has been used as evidence that sprouting could form recurrent inhibitory circuits and be a compensatory response to prevent seizures.

In the light of our current presentation, what is important about Sutula and Dudek’s [26] claim is that they propose that epilepsy is a “complex systems” disorder and recurrent excitation in the dentate gyrus reorganized by sprouting is an emergent property of a complex system, no matter which functional role is assigned to it. In a similar arena, the paradigm of kindling as a model of the epilepsies [27] linking plasticity to progression, and potentially to maladaptive phenomena or brain hyperexcitability, also seems to be a model of other clinical disorders such as anxiety, pain syndromes, obsessive–compulsive disorder, and depression [28]. Although comorbid conditions are common in patients with epilepsy, it is now more than obvious that the same nervous system might be the target of different pathologies that have different time courses. This is indeed clear-cut proof that the brain is a complex system and, if appropriately activated, some of its specific networks will produce different emergent properties. In other words, brain complexity can be expressed simultaneously in several disorders such as those mentioned, showing that the basic mechanisms are strongly similar to those for the epilepsies. On the other hand, a multitude of mechanisms can produce similar outcomes; for example, tonic–clonic seizures are a product of primary generalization in the so-called idiopathic epilepsies and a product of secondary generalization in the focal, partial epilepsies.

Following these two examples of the combination of complex systems and emergence in epileptogenic circuits [25,26], in this section I go further and put up for discussion results from our own experience with multilayered approaches and try to create a flux of ideas from what appears, at first glance, to be an apparently disconnected collection of data. Here I challenge our own approach showing how far we are from an actual integrative strategy to study the epilepsies and neuroscience in general. But at the same time, I emphasize that all along the path to discovery in epileptology studies, we are building up basic concepts and knowledge in brain function.

We constructed Figs. 1 and 3 quite schematically by combining the flux of information, in the form of texts of increasing levels of complexity, with reductions of increasing power (behavior, EEG, cells, axons, dendrites, molecules), along with a description of the main features of specific epilepsy models and their historical published records. Purposely, and in line with the main rationale for this review, we made the figures interact to graphically mimic a puzzle; therefore, the arrows, suggestive of the direction of the flux, indicate precise ensembles of pieces of the puzzle. No matter where you begin “reading” the puzzle, there are logical physical neighboring connections. Figs. 1 and 3 are composed of clear-cut statements and a given literature reference. At some point, each piece of the puzzle is self-contained.

Furthermore, the “textual puzzles” in Figs. 1 and 3 are “atomized versions” of the main features of different models and approaches, at some point extended in formats such as those in PubMed/Medline abstracts. Moreover, “image puzzles” (Figs. 2 and 4) are also “reduced figurative versions” of the set of figures contained in the cited references that accompany the text in Figs. 1 and 3. Figs. 2 and 4 are the mirror puzzle counterparts of Figs. 1 and 3, respectively, but now filled with images from the references cited in Figs. 1 and 3. Again, the purpose is that instead of only textual and historical records, we are presenting the images and actual data from the cited protocols, but without losing the neighboring connectivity. At some point this gives us the idea of dealing differently with texts and images, which is one of the main
Fig. 1. Puzzlelike graphic with textual and bibliographical recordings of sources of complexity and emergent properties suggested from experiments with the Wistar audiogenic rat (WAR) strain.

Fig. 2. Puzzlelike graphic with image recordings of sources of complexity and emergent properties suggested from experiments with the Wistar audiogenic rat (WAR) strain. With permission from Elsevier and Springer.
Fig. 3. Puzzlelike graphic with textual and bibliographical recordings of sources of complexity and emergent properties suggested from experiments with experimental models of temporal lobe epilepsy.

Fig. 4. Puzzlelike graphic with image recordings of sources of complexity and emergent properties suggested from experiments with the Wistar audiogenic rat (WAR) strain. With permission from Elsevier and Blackwell.
points of data sharing to be discussed later: textual information versus image information.

The puzzle metaphor means that in both texts and images, the physical pieces match each other perfectly. However, there is not a perfect match between the stories or between the image contents. The text tells a fragmented story made of truncated experiments and data, sometimes ameliorated with additional explanations (full articles are a good contemporary example). Historical links and interpolations help a lot; however, how much we know of the oldest methods, data collection and actual interpretation, could make the story even more complicated (review articles are a good example). The reconstruction of fragmented images is also not any better.

Specifically, in Fig. 1 (text) and Fig. 2 (images) are illustrated what we call sources of complexity and emergent properties, derived in this particular case from experiments done with animals of the Wistar Audiogenic Rat (WAR) strain. The data are arranged chronologically and methodologically with given levels of complexity, from behavioral to computational levels, in specific experimental epilepsy protocols. In each case, clear-cut statements of the relevant features of each model and associated publications are highlighted. To begin with, the WAR strain [29] was developed in our laboratory as a genetic model of sound-induced reflex epilepsy that, in the acute situation, models tonic-clonic seizures and, in the chronic protocol, models temporal lobe epilepsy (for a review, see Garcia-Cairasco [30]). At the behavioral level it is important to emphasize that all acute audiogenic seizures, not only in our WAR strain but also in other genetically developed strains, selected in several countries are dependent on the expression of brainstem networks (reviewed in Ross and Coleman [31]).

Also in Figs. 1 and 2, it is possible to observe that in addition to detailed behavioral studies with neuroethological tools [32], qualitative EEG alterations are also recorded [33] in acute seizures at the inferior colliculus level and in chronic seizures in the forebrain regions (see below). More recently we performed quantitative studies with the use of wavelet transform algorithm analysis of EEG data of acute and kindled audiogenic seizures [34]. Using the latter methodology we began neuropharmacological studies with the WAR strain and demonstrated that phenobarbital, acting mainly on GABAergic neurotransmission, was able to block audiogenic seizures when applied systematically, but not when infused into the substantia nigra reticulata, suggesting a potential genetic alteration in a critical component of an endogenous anticonvulsant system [35]. However, once the animal goes into a chronic protocol, the so-called audiogenic kindling [36], the newly evoked behavioral limbic seizures depend on activation of the recruited cortex, amygdala, and hippocampus [32,33,37-42].

At the circuit and cellular levels it is clear that audiogenic kindling is followed by positive (neurogenesis [39]) and negative (cell loss [41]) cellular alterations in the absence of Timm-positive mossy fiber sprouting [39,41]. Finally, at the molecular level (not shown in the figures), we are dealing with either hippocampal cultured cell populations of WAR strain rats [43] that exhibit failure in GABA and glutamate neurotransmission or hippocampal tissue homogenates from WAR strain rats [44], demonstrating endogenous and acquired alterations compatible with seizure susceptibility, such as increases in the expression of bradicaine B1 and B2 receptors.

Still, at the behavioral level, Garcia-Cairasco et al. [45] induced status epilepticus with subconvulsant doses of systemic pilocarpine in WAR rats, being a model of a combination of homogeneous genetic background (WAR) and limbic seizure experience.

Combination of the aforementioned behavioral, circuit, cellular, molecular, and computational environments gives us an enormous amount of information to deal with if our main question is integration and computational neuroscience. The progression from a genetically developed, brainstem-dependent acute audiogenic seizure to a newly induced, forebrain-dependent limbic seizure is at the same time a model for a complex system at all the levels mentioned and a model for dynamical emergent properties which fit quite well with the proposal made by Faingold [25].

Fig. 3 (text) and Fig. 4 (images) depict, at the circuit and cellular levels, what Tillelli et al. [46] demonstrated with the model of temporal lobe seizures described by Nissinen et al. [47]. Briefly, after 20-30 minutes of electrical amygdala stimulation, a self-sustained status epilepticus is induced that models NeuN-positive differential cell damage depending on the behavioral subtype of status epilepticus. This model is more severe than the amygdala rapid kindling protocol described by Ebert and Loscher [48] and reproduced with success in our laboratory by Foresti et al. [49]. Using the aforementioned model and quantitative EEG analysis by wavelet transform [34], we detected the expected afterdischarges and additionally secondary discharges, postictal and interictal spikes, in both hippocampus and amygdala. At the molecular level, Foresti et al. [49] showed that this rapid kindling protocol progressed despite zinc chelation.

Also at the cell level, Arisi and Garcia-Cairasco [50] used systemic pilocarpine to study, 1 month after the induction of status epilepticus, neuroanatomical alterations in the number of neurons, by means of stereology, and in dendrites of hippocampal granule cells, by computer reconstruction. At the computational level, Arisi and Garcia-Cairasco [50], using images from those epileptic animals, demonstrated by their presentation of at least one spontaneous recurrent seizure, and using the software Neurolucida [51], made three-dimensional reconstructions of the apical and basal dendritic branching of newly generated, doublecortin-positive hippocampal dentate granule cells. Epileptic animals had shorter but more branched patterns in their basal and apical dendrites. Those shorter and ramified apical dendrites ended mostly at the dentate granule cell molecular layer, exactly where the axonal collaterals of the mossy fiber sprout, suggesting a possible synaptic interaction between these two reactive structural changes, which needs to be proven by electron microscopy. Finally, and again trying to be selective in terms of limbic models, Furtado et al. [52] showed that intrahippocampal pilocarpine microinjection induces status epilepticus in Wistar rats, a protocol that renders zero mortality and that generates spontaneous recurrent seizures and hippocampal and amygdalar EEG epileptiform activity with strong hippocampal mossy fiber sprouting, which, therefore, represents another interesting model of temporal lobe epilepsy.

The most important issue I would like to discuss, derived from the content of Figs. 3 and 4, is the great amount of information that has been generated again at the behavioral, circuit, cellular, molecular, and computational levels that, if appropriately treated, can also be considered a complex system (limbic epileptogenic circuits) able to generate emergent properties (long-term plastic changes and spontaneous recurrent seizures and, therefore, epilepsy). Are not the EEG, cellular, and molecular changes that occur over time with seizures explanations of variations in behavior that consequently can be considered external markers of epileptogenesis? And, what about the behavioral correlates of differential lesioning patterns observed after self-sustained status epilepticus induced by electrical stimulation of the amygdala? What are the functional implications of the described dendritic pattern alterations in newly generated granule cells after pilocarpine-induced status epilepticus?

As a whole these data also fit the proposal recently made by Sutula and Dudek [26] if we take our data and their data as specific examples of complex systems that generate dynamic emergent properties. To go forward in terms of potential solutions, in the next section I address current strategies that deal with complexity.
not only in normal situations but also in neuropathological conditions such as epilepsy.

4. Current strategies to deal with complexity and emergence in epileptology and in contemporary neuroscience

A contantly growing set of mathematical, statistical, and computational tools are currently available to deal with strategies such as general algorithms in nonlinear dynamics, neural network modeling, small-world networks, graph theory, and EEG prediction signatures, among others. However, it is not my intention in this short review to delve into the details of those methodologies. At the same time I introduce, from our point of view, the need for integration in experimental designs (either wider or reductionistic), in methods of data collection and their interpretation, in neuroscience and in epileptology in particular, I finish by turning the discussion to strategies and solutions, mainly with highly complementary, statistical, mathematical, and computational algorithms, tools, and developments. Toward that end, I discuss briefly a sample of these current methodologies.

At the behavioral level, I begin by presenting interesting data derived from the development of Animats by Watts [53], who describes these as computer-simulated animals or robots that interact with the real world. Animat simulations are considered inexpensive and powerful tools with which to study behavioral mechanisms. Behavior-based artificial intelligence uses Animats capable of autonomous and adaptive activity as conceptual tools in the design of useful intelligent systems. With clear implications for bioethics because of the consequent reduced use of experimental animals, Watts [53] suggests future use, probably applicable to neuroscience and epileptology in particular, in “modeling animal movement during human handling and the effects of environmental enrichment on the satisfaction of behavioral needs” (my highlight).

Ohayon et al. [54] developed a network analysis impinging on an external robot with interactive states, determined by sensors and motor output, that can mimic either normal (point-fixed) or epileptic (oscillatory with seizure-like motor output) behavior. The dynamics of the interactive network—autonomous agent complex was effective in discriminating normal from pathological conditions, bringing to the field of epileptogenesis modeling an attractive framework that incorporates computational and intelligent tools to distinguish healthy from epileptic networks. In more technical terms, they describe stand-alone and embodied (autonomous agents) modeling using fully interconnected recurrent neural networks with unit self-feedback. The embodied recurrent network approach discriminates intelligent behavior (computational viability) or pathological conditions (limit cycles or fixed point regions).

Our main interest and one of the major preoccupations of the study, as expressed by the authors, was “to focus the search of network space to identify networks with more complex dynamics. Here we rely on a major available indicator critical to clinical assessment but largely ignored by epilepsy models, namely: behavioral states” (my emphasis) [54]. Because of the predictions and results from the model, Ohayon et al. [54] also state that “these observations turn the question of what causes epilepsy on its head. Instead of asking how epilepsy comes about, they compel us to ask how recurrent neural ensembles ever manage to avoid this ubiquitous synchrony in the first place. That is, why are we not all epileptic, all the time?” The latter statement matches exactly what we have been asking in the analysis of our experimental [30] and even clinical data [55] over the last two decades: It is more complicated to explain how more than 98% of the world population is not epileptic than why and how only less than 2% of the same population have epileptic seizures. At some point this was more evident when we began to experimentally study the so-called endogenous anti-convulsant systems [35,56] and their impact in clinical epileptology in [57], in the majority of the mentioned cases with strong quantitative behavioral analysis, which is quite a real-biology complement of the computational and network approach developed by Ohayon et al. [54]. Although we have done extensive work with neuroethical tools in experimental [30] and, more recently, clinical seizures [55,57], we in fact made no actual computations of the time and frequency series represented by behavioral seizures. Certainly, complexity measures and spectral analysis of graphs, as well as small-world networks, will be plausible strategies to characterize those phenomena.

At the circuit level, further computational approaches have been introduced by Lungarella et al. [58], who propose that dynamic coupling between sensory and motor systems can be studied by characterizing the ability of embodied agents (organisms and robots) to actively structure their sensory input and to generate statistical regularities. The latter are extremely important, for example, for developmental processes, adaptation, and learning.

To understand sensorimotor coordination, these authors developed statistical measures useful in quantifying information structure in sensory and motor channels of a robot capable of saliency-based attentional behavior. At the same time that Stam [59] applied nonlinear dynamics protocols to the study of epilepsies at the transition from the interictal to the ictal state, Adeli et al. [60], using wavelet-chaos algorithms, discriminated seizure types using parameters that represent either system complexity (correlation dimension, CD) or system chaoticity (largest Lyapunov exponent, LLE), in comparing subjects from three groups—healthy, epileptic not during seizures (interictal interval), and epileptic during seizures (ictal)—the CD discriminates the three groups with respect to the higher-frequency beta and gamma subbands, whereas the LLE does this for the lower-frequency alpha subband. Also, at the circuit level, Iturria-Medina et al. [22] studied the probabilities of anatomical connections between cortical and subcortical brain gray matter areas estimated from diffusion-weighted magnetic resonance images. In other words, they performed brain modeling as a nondirected weighted graph derived from anatomical connection probabilities matrix. With this in hand, they claimed that the proposed networks with small-world and broad-scale characteristics have larger local efficiency and smaller global efficiency when compared with random networks.

Moreover, at the cell level, Butz et al. [61] worked with artificial neural networks that simulate activity-dependent synaptic reorganization with changing numbers of neurons, synaptogenesis in a recurrent network, recombinations, cell proliferation, and apoptosis. They produced a network that models dynamic remodeling of connectivity patterns by cell proliferation and corresponding neurogenesis, apoptosis, and synaptogenesis, focusing more on structural and systemic effects of cell proliferation than on computational properties.

At the molecular level, it is possible to find algorithms that have been developed to evaluate massive collections of data such as those currently approached in genomic and proteomic studies [62,63]. Specifically, Liu et al. [63] made an interesting study of the proteomic characterization of the hippocampus after status epilepticus induced by systemic pilocarpine in rats. Basically, they used comparative proteomics and projection of signaling networks to facilitate simultaneous detection of expression of considerable amounts of proteins validated as potential biomarkers for epilepsy therapies. They applied the Ingenuity Pathway Analysis to associate proteins detected by proteomics, Western blot, and immunohistochemistry with their biological functions and ended up with hippocampal expression of a significant group of proteins arranged in networks based on their relationships with biological functions.
5. Neuroinformatics and e-neuroscience

The exponential manner in which we are accumulating research results is a strong argument for developing completely different methods not only of producing data but also of storing and sharing data [64]. This whole issue has explained how the so-called Neuroinformatics Projects need to be implemented and spread worldwide. In other words, once we have produced the data, we need to store them somewhere, in an easily reachable place, where the main goal of the neuroinformatics—sharing—will be possible.

In an interesting article entitled “What Will Save Neuroscience?”, Bower [65] states “It is my view that what is needed is a fundamentally new paradigm for data evaluation and communication within neuroscience” and ends with “For our field to advance, we must move from a point of view in which each of us is working with our own personal, internal, unquantified, and therefore largely untestable model of how “our” part of the brain works, to shared, quantifiably testable models. It is my view that realistic neuronal models are ideal for this purpose, representing a compact and self-correcting association of neurobiological facts and functional relationships.” Another important point Bower [65] makes is the need to promote sharing of interpreted and analyzed results instead of simply collections of data to be browsed and downloaded with respect to the specific criteria of the users, which in many cases is time consuming and simply useless.

An excellent example of data sharing was proposed several years ago, and although still not at a level corresponding to the number of researchers expected to join these projects, it is consistently growing. Recently, one of its promoters, Giorgio Ascoli, has extended his efforts by discussing strongly what the advantages of sharing morphological neuron data are, for example, three-dimensional reconstructions using current imaging tools and the difficulties or fears alleged by most of those who do not share their data [66,67].

Specifically, Ascoli [66] states that the success and prestige of molecular biology laboratories are measured as a proportion of their shared data visibility, whereas in neuroscience, this is still quite a poor routine. However, in a good sense, several projects have over time increased support of neuroinformatics initiatives, among them the Human Brain Project [68] and the NIH Blueprint Initiative [69]. In addition, Ascoli states that data sharing also means open-access publishing so that data should become available quickly and freely to the scientific community. A natural consequence, he ends, is that collaboration, coordination, and computation should yield data, tools, and resources needed by neuroscientists.

One additional point Ascoli [66] makes is that data sharing is getting easier because currently we have available a large number of free software tools for digital neuronal morphology, such as NEURON [70] and GENESIS [71], in addition, for example, to commercial products such as Neurolucida [51], that are used for digital two- or three-dimensional reconstructions. Lists of these tools, which are continuously updated, are available through Neuroscience Database Gateway [72] and Neuron_Morpho [73] from the Krasnow Institute.

The Organization for Economic Cooperation and Development (OECD)’s Neuroinformatics Working Group [74] also emphasizes that there is significant interest among neuroscientists in sharing neuroscience data and analytical tools. This group strongly believes that in addition to small accessible database initiatives, specialized analytical software, and modeling tools, large-scale international collaboration is needed to improve coordination and funding, because in their words: “data sharing will play a pivotal role in human brain research and lead to innovations in neuroscience, informatics and treatment of brain disorders.” In the same direction, the UK Code Analysis Repository & Modelling for eNeuroscience (Carmen) Project [75] is considered a virtual laboratory for neurophysiology, enabling sharing and collaborative exploitation of data, analysis code and expertise that are not physically colocated. Neural activity recordings (signals and image series) are the primary data types.

In the field of genomics in epilepsy research, among other examples, the National Institute of Neurological Disorders and Stroke (NINDS) held the DNA Microarrays and Epilepsy Research Meeting in 2005, the main recommendations and conclusions of which were, first, to establish the NINDS Task Force on Multi-Laboratory Consortium for Microarray Experiments in Epilepsy and, second, to use the microarray centers because of their expertise to eliminate sources of experimental variability.

As a further comment in this regard, Insel et al. [76] strengthen the view that ambitious projects such as transcriptional brains, genomic projects, and other goal-directed or large-scale research projects will obligatorily imply the transdisciplinary collaboration of scientists mainly in the field of computational neuroscience, where the fundamental issue is that of meaningful data sharing.

As an initial effort in the field of data sharing, our laboratory has contributed recently in the context of research directed at the three-dimensional reconstruction of newly generated doublecortin-positive dentate granule cells after status epilepticus induced by systemic injection of pilocarpine. The final step, besides having the whole set of experiments published [50] was the uploading of those three-dimensional reconstructions in the NeuroMorpho Project [73] at the Krasnow Institute. At the electrophysiological level, we have also developed tools to perform EEG quantitative analysis of sleep and epilepsy data [34]; the algorithms are also available on the Web. With these efforts, we are also, slowly but steadily, contributing to this new era of contemporary neuroscience, in which data sharing is the fundamental cornerstone.

6. Conclusions, challenges, and perspectives

To make a significant change in paradigm, we need to accept the need for a turning point in our expectations about science in general and neuroscience in particular. However, whatever the specific analysis we are dealing with in neuroscience and, in this case, epileptology studies, from the behavior to the circuit to the cellular, molecular, and computational levels, the endpoint will always be the human interface, who decides, we hope wisely, how to approach, either reductionistically or not, we hope in integrative form, with transdisciplinary strategies, how to conduct experiments and research programs. In addition to the numerous, widely available, easily accessible data collection methods, new tools, new technologies, and groups that are eager to collaborate can be easily located and recruited today.

In line with our puzzle metaphor, the current universal gigantic puzzle of neuroscience knowledge, probably composed of trillions of small pieces, requires similarly gigantic computational tools and transdisciplinary efforts simply to figure out where to start. To obtain precise ensembles (solutions to the puzzle) will require the formation of consortia in specific subdisciplines such as neuroinformatics and e-neuroscience.

In a practical exercise, Fig. 5A–C illustrate probable scenarios for puzzling challenges in contemporary neuroscience. Figs. 5A and B show what I call the perfect physical, textual, historical, and image puzzle. You can think of it as something already existent (text puzzle and consequent logical story, see Fig. 5A), but cut in pieces afterward. In the case of Fig. 5B, instead of a text puzzle we have an image puzzle. How much of these “perfect puzzle metaphors” are contained in science? What about a variation with a melted image puzzle (Fig. 5C)? Is not the latter, at some point, the confound-
It is interesting to note that our view resonates with the concepts of the two cultures, scientific/artistic and scientific/literary, and the so-called scientific revolutions at some point discussed by Snow [77] and Kuhn [78]. This view also resonates with the already mentioned concept of consilience or the “unity of knowledge” of Wilson [13] because it refers to closing the gap between the two cultures. All of these propositions and discussions have been, to some extent and at their own times, highly acclaimed and highly criticized; however, reappraising them shows how true they are.

In that sense, I make one particular and final comment on The Structure of Scientific Revolutions, by Kuhn [78]. Basically he states that science does not progress via a linear accumulation of new knowledge, but undergoes periodic revolutions, also called “paradigm shifts,” in which the nature of scientific inquiry in specific fields is abruptly transformed. This so-called revolutionary science is the consequence of a chain of events where “prescience,” without any paradigm, is followed by “normal science.” In the latter, the central paradigm is enlarged by scientists by “puzzled solving.” If there is accumulation of results/paradigm mismatching, the paradigm is not refuted but the anomalous result is considered a researcher mistake. After a consequent crisis, if the amount of anomalous results increases, a new paradigm is accepted based on the critical combination of old and anomalous results into one newly-emerged framework.

7. Conflict of interest statement

The author here declares that the development of this study does not imply any kind of conflict of interest.

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Fig. 5. Puzzlelike graphics. Top: Perfect physical, textual, historical puzzle. Middle: Perfect physical, image, historical puzzle. Bottom: Melted, imperfect physical, textual/image, historical puzzle. With permission from Elsevier and Blackwell.


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