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Therapeutic Neuromodulator in The Direction of a Critical State can be used as a General Treatment Strategy

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Abstract

One of the most pressing health issues of the 21st century is brain disease, which necessitates the development of novel, more efficient treatments.In order to treat a disease, neuromodulation is an excellent method for altering the activity of various neuronal regions.The idea that deficiencies in systems-level structures like brain waves and neural topology are the root cause of neurological disorders has led to an increase in the number of medical indications for neuromodulation therapy.Based on patterns of synchronization among neuronal populations, it is hypothesized that connections between neuronal regions fluidly form and then dissolve again.In comas and seizures, respectively, similar hypersynchronization and igniting of the brain's activity can occur.This is like a fire that can either get bigger or go out completely.Interestingly, however, in a critical state where neuronal activity maneuvers local and global operational modes, the healthy brain remains tucked in between these extremes.Although it has been suggested that disruptions in this criticality may be the root cause of neuropathologies like schizophrenia, epilepsy, and vegetative states, no significant translational impact has yet been achieved.Recent computational findings presented in this hypothesis article demonstrate that the critical regime is maintained by a neural network's short- and long-range connections in distinct but manageable ways.Long-range connections determine the scope of the neuronal processes, whereas short-range connections shape the dynamics of neuronal activity.Therefore, we introduce topological and dynamical system concepts within the criticality framework and discuss the implications and possibilities of therapeutic neuromodulation guided by topological decompositions to facilitate translational progress.

Keywords: Criticality; Small World; Neural Network; Simulations; Neuromodulation; Therapy; Self-Organized Criticality; Oscillations; Brain Waves; Translational; Tms; Tdcs; Dbs; Vns

Introduction

Considering the extraordinarily complex arrangement of the nervous system, the neuronal dynamics to which it gives rise, and the plethora of ways in which it can go wrong, neurological disorders have emerged as one of the greatest challenges to social and health care systems of this century, costing more than 800 billion EUR annually in Europe [1]. This is not surprising given the complexity of the nervous system. More efficient clinical strategies must be developed immediately to address this growing issue [2].

Neuromodulation is a technique for adjusting the activity of specific nervous system regions or cell types.In recent times, numerous neuromodulatory techniques have been developed.Some, like optogenetic modulation, have seen significant clinical application, while others remain largely in the realm of fundamental science.In fact, spinal cord and peripheral nerve stimulation for chronic pain relief, transcranial magnetic stimulation (TMS) for depression, and deep brain stimulation (DBS) of the basal ganglia for Parkinson's disease are among the most well-established neuromodulatory treatments currently available [3]. Neuromodulation therapies have proven particularly appealing in pharmacologically resistant diseases where drugs are either ineffective or have unacceptable side effects. Neurosurgeons can use targeted techniques like stereotaxic DBS and MR-guided focused ultrasonography (MRgFUS) to delicately modulate or ablate specific neuronal populations while protecting the organism as a whole from unintended strain. MRgFUS-thalamotomy can now be used to treat essential tremors, removing patients from the traditional beta-blocking regimen, which is associated with significant risks to cardiopulmonary physiology, including bradyarrhythmias and respiratory failure. Translational neuroscientists are expanding the medical applications of neuromodulation therapy [4]. Researchers are increasingly adopting a holistic approach to nervous system pathology in accordance with systems neuroscience theories.According to systems neuroscientists, neurological disorders like epilepsy are fundamentally caused by deficiencies in systems-level structures and rules like the functional topology and brain wave coherence of the neural network. For instance, pain relief through spinal cord neurostimulation represents a remarkably effective treatment for chronic pain syndromes, significantly reducing the need. The idea that cerebrum waves play a crucial role in the mind's utilitarian engineering is supported by growing consensus.To support this fundamental role, brain waves have been linked to a surprising variety of neurological processes. These processes include the rehabilitation of consciousness through peripheral vagus nerve or thalamic stimulation, the alleviation of schizophrenia through prefrontal TMS, or Memory formation, spatial and cognitive navigation in the hippocampal formation, sensory perception, and consciousness throughout the cerebral cortex [5-9]. Based on the distinct patterns of coincident neuronal population activities, it has been hypothesized that neuronal communication between distributed neuronal regions forms and dissolves rapidly and flexibly.

The brain's ever-changing activity can become hypersynchronized and self-amplify, like epileptiform seizures, or it can diminish in dissonance and become stale, like in a coma. This is like a fire that can either get bigger or go out completely. It is remarkable, however, that

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the normal brain remains tightly wedged in between these dynamical extremes in a state known as the "critical state," where neuronal activity maneuvers both local and global modes of operation.Neuropathological conditions like schizophrenia, epilepsy, and disorders of consciousness (DoC) have been linked to disruptions in this criticality of the brain system [**10**]. Despite its obvious clinical potential, the theory of criticality has not yet had a significant impact on the translation of neurological care.

A neural network's critical state is maintained differently by short- and long-range connections, according to recent computational findings from our lab. While short-range connections have an impact on the dynamics of neuronal activity, long-range connections ultimately determine the scope, or state, of neuronal processes. By targeting distinct neural network topology components, this insight makes critical systems theory tractable as a general therapeutic strategy for neuromodulator [**11**]. The gap between clinical practice and theory must be bridged in order to facilitate translational research in this field. In order to accomplish this, we discuss the implications and possibilities for neuromodulation therapies after providing an introduction to topological and dynamical systems concepts within the framework of criticality. This article focuses on disorders like DoC and epilepsy that affect neuronal activity at the systems level due to the inherent systemic scope of critical dynamics [**12**].

The Critical State and a Neural Network's Topology [13]

In point of fact, a neural network can be wired in a number of different ways, and the topology of the network is ultimately determined by each method. The way neuronal nodes connect has a significant impact on the information processing capacity of the neural network.Take into consideration the scenario in which each node is connected to its k closest neighbors in a unique way. By creating a lattice of the same repetitive pattern here, all parts of the network become identical:It is said that the network is perfectly organized. In turn, we define the opposite extreme, which is known as perfectly disordered, by randomly wiring all network connections.

The fully ordered network, on the other hand, contains segregated clusters of nodes with few to no long-range interconnections, as measured by graph scientists by the extent to which the nodes cluster (transitivity). Through the use of long-range shortcuts to connect distant parts of the network, we discover a crucial arrangement in between these extremes that maintains the clustering of ordered networks and provides a low nodal separation. On the other hand, the disordered network is characterized by sporaThis semi-random arrangement, which Watts and Strogatz referred to as "small-world" in reference to Stanley Milgram's experiments on social networks and the six degrees of separation phenomenon, was dissected in their seminal 1998 paper. The state of a system that is close to undergoing a qualitative transformation, also known as a significant shift in the behavior of the system, is known as the "point of criticality" of the small-world system. It acquires characteristics exclusive to the states that bind it here.

How does the structure of a network affect the signals that pass through it?For instance, signals begin to spread beyond the local span and eventually saturate global network activity when nodes are more interconnected. It has been demonstrated that as topological separation increases, signals cluster together locally as a result of long path lengths' resistance to global transmission.Near the small-world criticality, the signals are more likely to reverberate through global and local activity patterns.This is comparable to the way that activity in the brain shifts over various spatial scales: one moment, it is mostly localized, and the next, it spans global assemblies that are interacting with each other. To put it another way, it would appear that when the brain enters the critical state, it can change its operational mode to accommodate either local or global computational scopes whenever this is needed. Cocchi and his coworkers make the succinct observation that follows: Execution of particular tasks is one aspect of brain function; context and objectives influence adaptive switching between functions.As a result, there has been widespread speculation that the topology of the brain is similar to architectures of small worlds.

Systemic brain disorders like insomnia, schizophrenia, and epilepsy may result from deviations from the critical state, which has a high dynamic range, efficient information capacity, and high information transfer fidelity. Seizures, from this point of view, are states of global neuronal hypersynchrony, or super-criticality.In contrast, schizophrenia is a type of subcritical network dynamic in which long-range communication is underutilized and neuronal activity remains poorly coordinated. A DoC is a network state that is clinically characterized by a persistent deficit in consciousness and is pathologically subcritical.Formally, DoCs are categorized as minimally conscious, vegetative, and comatose according to the degree to which their neuronal activity becomes weaker and more fragmented.As a result, understanding the nature of brain pathology and potential future treatments could greatly benefit from examining the human brain as a system operating close to criticality.

If critical systems are not disturbed, they should theoretically remain so for an indefinite amount of time.In practice, however, the critical state resembles an unstable equilibrium in dynamical systems theory, where any naturalistic system is forced to extreme states by stochasticity and noisy disturbances. According to Hesse and Gross, the brain must have mechanisms for maintaining and transitioning through the critical state, also known as the neuronal implementation of self-organized criticality. This is based on the tendency.

Long-Range Neuronal Connectivity Defines the System's State [14]

The system's state is determined by long-distance neural connections; consequently, a criticality state could be maintained and moved by modulating the long-range connectivity of the network. In point of fact, while high levels of long-range connectivity cause hyper-synchronous seizures, low levels of long-range connectivity stifle global neural network interactions (sub-criticality). Therefore, it is reasonable to anticipate that a sudden halt in global network activity will result from a significant disruption in the brain's long-range connectivity. Consequently, neuropathologies marked by critical state deviations should, intuitively, manifest as a loss of consciousness. Traumatological findings suggest that a disruption in long-range neuronal connectivity could result from impairments in global neuronal coherence caused by damage to the thalamus or its neuronal prerequisites in the brainstem.This finding has been attributed to the reticular activating system in the brainstem, which controls the thalamic nuclei that are responsible for long-range cortico-cortical synchronizations via thalamo-corticothalamic loops. Patients in vegetative and comatose states typically have damage to the thalamus or its relays, but not to the cerebral cortex itself, which lends credence to this theory. In addition, the thalamus may not be necessary for consciousness at all because, at least in a rodent animal model, its complete ablation does not result in unconsciousness. This is the case despite the fact that thalamic lesions are consistently associated with DoC in humans. This necessitates additional research into the functions that neuronal diaschisis plays in specific brain regions like the thalamus and basal ganglia as well as

global network connectivity.The idea that consciousness can only be sustained at a certain minimum level of long-range connectivity, also known as global neuronal interactions, is fascinating.The mechanisms of SOC may actually become null when this threshold is crossed, making it impossible for the brain state to escape the subcritical or unconscious state and reach criticality. In a similar vein, it has been demonstrated that severely disabled patients who are still conscious tend toDBS of the thalamus typically results in limited behavioral improvements in patients with severe DoC, which get worse before treatment. Similar results are seen with amantadine, a neurostimulant that helps global cortico-thalamic loop interactions by freeing thalamic nuclei from pallidal inhibition. On the other hand, patients with mild to moderate DoC have had remarkable success, supporting the idea that successful rehabilitation.

Merits of Combinatorial Neuromodulation Strategies [15]

Because the activity of the neural network can be divided into dynamic and static drivers, combinatorial neuromodulation strategies that target both the short- and long-range topological domains of the network can be tested.Indeed, the synergic potential of differential topological modulation that is suggested by computational analyses lends credence to the distinctive pattern of neuronal hyper-connectivity that is frequently observed in the brain following neuro-trauma. Combinatorial neuromodulation research has primarily focused on antidepressant therapy, which has demonstrated remarkable efficacy in this indication. Potentiating cortical excitability through TMS and long-term VNS has been shown to significantly improve coma recovery scores in moderate DoC. It has been hypothesized that this hyper-connectivity is a sign of a compensation mechanism related to an injury. Through enhanced short-range neuronal connections, we hypothesize that this mechanism may stabilize the critical state. A recent pilot study by Bender Pape and colleagues found that treating depression patients with TMS prior to amantadine doubled their behavioral gains. However, little research has been done on the effects of antidepressants. This indicates that the testing of combinatorial neuromodulation techniques outside of conventional therapeutic settings should be expanded in subsequent research. By making it simpler to maintain criticality through adjuvant long-range potentiation, such as DBS of thalamic nuclei, this strategy basically aims to stabilize the system's dynamic.In the treatment of post-traumatic DoC, where combined short- and long-range neuronal injuries are more likely to be the cause of pathology, this kind of combinatorial paradigm may be especially useful.Examples of short-range neuronal potentiation include TMS, tDCS, and VNS.

Our primary focus has been rehabilitation of pathological brain states and brain dynamics up until this point.It is essential to keep in mind that topologically guided neuromodulation may also be useful for non-therapeutic purposes. By facilitating subcritical and sedative system states, for example, a deliberate destabilization of the dynamics of the brain's systems could be used to enhance the effects of general anesthesia.A sophisticated closed-loop neuromodulation technology that responds to ongoing neuronal activity could be developed by incorporating the framework of topological decompositions into the architectures of deep neural networks.Surgery-related complications like cardiopulmonary failure and urinary retention may therefore be less likely to occur.For future research, it is necessary to conduct a more in-depth examination of the neuroelectric effects of topologically differentiated neuromodulation, such as high-density ECoG. A critical systems approach to neurotrauma may also aid in the development of strategies for acute management. Due to the SOC mechanisms being essentially overcome by excessive topological propensities, this could, in severe cases, ensnare the brain in a state of persistent unconsciousness. Through subacute neuroplastic changes like Hebbian rules that reduce general synaptic gain, we hypothesize that a trapped state could get worse or become functionally irreversible.However, in order to test strategies for reducing both acute mortality and long-term patient outcomes, future research needs to clarify how neurotrauma affects critical system dynamics.This raises concerns regarding the advantages of neuroprotective measures like hypothermia and induced coma, which prolong central nervous system depression.In this case, quantitative EEGs may be used to continuously assess the patient's neuroelectric status.

Conclusions

In conclusion, this hypothesis article has demonstrated the connection between the neuronal dynamics that pervade a neural network and its topology.We argued, in particular, that the neurocomputational scope of the brain's functional topology is continuously optimized and adapted by short- and long-range neuronal synchronizations. The hypothesis of a functional division of network topology based on the length of neuronal connectivity is supported by ample empirical evidence; however, causal data are required for critical systems analysis of neuronal responses to neuromodulation. Future research ought to focus on improving our comprehension of topological system decompositions because differential neuromodulation may be involved in the prevention and treatment of systems-level human neuropathology.

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