Chapter

Introductory Chapter: Neurostimulation and the Structural Basis of Brain Activity

Denis Larrivee

1. Introduction: neurostimulation and global organization

Despite its remarkable clinical efficacy and several decades of use, neurostimulation remains a therapy whose neurophysiological basis is yet undetermined [1]. This lack of basic scientific understanding has imposed a conceptual barrier that has broader implications for therapeutic efficacy. Nonetheless, an improved understanding of the mechanisms of brain activity, observations on the etiological basis of neurological diseases, and insights from diverse therapeutic applications offer hope for understanding how the therapy physiologically impacts neural impairments.

Because the form of neurostimulation is rhythmic, it has been suggested that neural mechanisms responding to stimulation are similarly rhythmic [2]. Rhythmic activity is notably ubiquitous in brain operation, and has been observed in single neurons that display patterned spiking, as well as at network levels, where variable inhibitory and excitatory feedback configure repetitive activity [3]. Increasingly, these are proposed to be oscillatory [4]. Significantly, oscillators are prone to pairing and can combine in an indefinite number of permutations to recreate encoded feature representations. The therapeutic role played by neurostimulation thus plausibly entails oscillatory interactions, where neurostimulation could modify dysfunctional oscillations, presumably by altering their intrinsic features, like patterning, synchronization, and desynchronization. Recent studies show in fact that brain activity is globally structured through oscillatory interactions, with key elements distributed throughout the brain. Such elements would be expected to be similarly perturbed in various impairments; hence, restoring normal function would require that they be reconstructed.

Consistent with this proposal, it is known that global brain activity is coordinated by slow frequency oscillations that resonate between subcortical and cortical regions [4]. These activity structures mediate organismal functions, which are cohesively ordered to the good of the individual; hence, their investigation can be expected to provide a basis for understanding the higher order organization that underlies brain dynamics at global scales. Indeed, without such understanding, the effects induced by neuromodulation and neurostimulation remain anecdotal and their utility to therapeutic design uncertain.

How then is global brain activity affected by neurostimulation? Some insight into this question can be expected from the study of diseases known to disrupt global brain events. One candidate is epilepsy, which has been treated by neurostimulation for several decades. Significantly, a characteristic feature of epilepsy is the occurrence of epileptogenesis outside initial seizure foci. The processes associated with this distribution are not known, but current evidence implicates

contributions from both higher order cognition and homeostatic mechanisms, that is, top-down and bottom-up factors that amplify and spread local seizures. This chapter will review current work on these processes, some of which associate with consciousness and default mode network operation, with the expectation that they are also likely to be found in other disease states. Their characterization is thus likely to inform intervention in other medical disorders and so enhance the efficacy of neurostimulation for an increasingly diverse range of cognitive impairments.

2. Epilepsy as a paradigm for global perturbation

Epilepsy is a widely occurring, common neurological disorder. After stroke, it is the second leading brain impairment, affecting nearly 50 million people worldwide [5]. Epilepsy has been defined by the International Bureau for Epilepsy (IBE) as a "disorder of the brain characterized by a persistent predisposition to generate at least one epileptic seizure and by the neurobiological, cognitive, psychological and social consequences of this condition" [6]. Seizures may also cause various sequelae that can entail brief changes in perception and behavior, mild convulsions, and temporary loss of consciousness, which appear to relate to seizure origin and the degree of their intensity. The neurophysiological factors leading to these sequelae are currently unknown. On the other hand, it is known that epileptogenesis affects brain areas well beyond the epileptogenic foci [7]. The domains affected, their mechanisms of spatial distribution, and the nature of disturbance are thus likely to be significant factors in generating the variability observed in epilepsy's symptoms. Among the often profound changes occurring during epileptic episodes, for instance, are altered states of consciousness, which are likely to involve major networks outside the region of seizure origin. Consistent with such observations, functional connectivity is impaired in large-scale brain networks that extend both bilaterally and via subcortical structures [8]. For recurring seizures, therefore, large-scale interactions could be major pathogenic factors contributing to symptom severity.

Findings from patients resistant to treatment with anti-epileptic drugs, in fact, strongly suggest this. Because the probability of resistant patients to achieve complete remission with new antiepileptic drugs is less than 10%, surgical intervention is often considered the best option for treating intractable epilepsy [9]; however, after temporal lobe and/or localized neocortical resections, only 29–65% of the patients are free of seizures. This relatively low success rate has prompted a number of studies on the mutual, excitatory, and inhibitory interrelations of brain structures participating in epileptogenesis, which have converged on a proposal of epileptic systems that develop in the brains of these patients. The existence of such complex epileptic systems could explain the intractability of epilepsy and the lack of success of resective surgery.

2.1 Impaired homeostasis and the globalizing of epilepsy

How extra-focal, ictal activities emerge in the epileptic brain is still unknown. However, since many of the factors contributing to epileptogenesis, such as stroke or trauma, likely affect homeostatic mechanisms, it has been suggested that included among the chief etiological factors are those related to impaired preservative or homeostatic processes [10]. Fasting, notably, has long been known to have an anticonvulsant effect. The discovery in the 1920s that the anticonvulsant activity was due to ketosis led to treatments using strictly altered diets, for example, the ketogenic diet. Consistent with the results of these dietary studies, conditions precipitating epilepsy like traumatic brain injury, and diseases with which epilepsy

is often comorbid, like Alzheimer's, exhibit a chronic loss of energy homeostasis. Moreover, energy levels are acutely impaired during seizures or their precipitating events. Since energy homeostasis is clearly a global requirement, its impairment is likely to contribute to the spread of epileptic foci.

Since the discovery of the effect of fasting on epilepsy, many studies have confirmed the essential participation of metabolic dysregulation and the imbalance of energy metabolites in the disease. During seizures, for instance, the rates of glucose and oxygen consumption rise [11], requiring more energy than that produced by oxidative phosphorylation via the TCA cycle. Glycolysis, consequently, replaces oxidative phosphorylation as the main supply of neuronal ATP. Enzymes involved in the TCA cycle, such as aconitase, malate dehydrogenases, and succinate dehydrogenases decrease their activity during seizures, whereas those involved in anaerobic glycolytic metabolism, such as phosphofructokinase and glucose kinase, increase. The fall in oxygen levels occurring during seizure hyperactivity also induces the expression of hypoxia-inducible factors (HIFs), further exacerbating the inhibition of the mitochondrial TCA cycle and the preferential activation of glycolysis. Glycolysis, however, is insufficient to sustain the hypo-polarization required for preventing spontaneous axonal firing, which is mediated by the energy-demanding sodium-potassium-ATPase (Na^+/K^+-ATPase) enzyme. Na^+/K^+-ATPase malfunctioning, for example, has been shown to result in neuronal hyperexcitability, and to be involved in post-seizure extracellular K^+ clearance and in neonatal seizures [12].

Additionally, with the onset of seizures, the rapid drop in ATP results in a corresponding elevation of adenosine that can exceed baseline levels by more than 40 times [13]. Adenosine, significantly, is a key regulator for energy homeostasis in cells. Its rise, due to ATP depletion, serves as a negative feedback regulator that attenuates cellular activities that consume energy. The rise in adenosine in neurons, particularly, has been shown to attenuate cellular ATP-consuming processes directly related to neural function. Among its effects is a receptor-mediated inhibition of synaptic transmission in the brain [14]. The presynaptic adenosine-1 receptors (A1R), for instance, inhibit synaptic release of most neurotransmitters, especially those used for excitatory transmission. Significantly, a pathological hallmark of epilepsy is astrogliosis, which has been linked to the overexpression of adenosine kinase (ADK) and the consequent adenosine deficiency. Consistent with this observation, a fall of 25% in adenosine is measured by microdialysis in epileptogenic zones. Increased ADK expression, furthermore, results in the spontaneous occurrence of seizures, whereas ADK reduction in the cortex and hippocampus of transgenic mice confers resistance to seizures and to epileptogenesis. Cumulatively, impaired adenosine metabolism—and the specific impairments to aerobically generated energy metabolites appear as key factors leading to epileptogenesis.

2.2 Epileptogenic recruitment and energy impairment

An important aspect of the generation of epileptic seizures is the recruitment of substantial regions of cortical tissue into pathological activity. Given a progressive spreading of metabolic impairment, recruitment can be expected to consecutively engage nearest neighbor, neuronal circuits. On this basis Wang et al. [15] posited a model of interacting minicolumn arrays distributed across a cortical tissue sheet, which sequentially evoked epileptogenic activity. Their model generated focal zones of hyperactivity within the simulated sheet, an observation consistent with microperiodic epileptiform discharges seen during interictal intervals in epilepsy. The high activity zones recruited first neighboring and, later, distant sites, eventually leading to abnormal activity throughout the whole sheet. The time required to recruit the whole sheet depended on the number of hyperexcitable clusters, with earlier

recruitment occurring when more clusters were present. Together, the model's predictions were consistent with some notable observations seen during epileptogenesis.

Among the chief mechanisms likely to account for the global activation seen in these results is that of spike timing-dependent plasticity (STDP), where units neighboring epileptic zones experience localized and synchronous depolarizations coinciding with the depolarization occurring within the zones [3]. With STDP, epileptogenesis would be expected to initiate synchronized activity focally, followed by a progressive advance to larger and larger cortical areas. Indeed, it has been presumed that ictal episodes lead to recruitment through processes of synchronization.

Such synchronization has been shown to occur during the late phases of seizure discharge. Seizure initiation and interictal epileptiform events, however, are not consistently associated with synchronous activity, as would be expected if synchronization were chiefly due to localized effects of spike timing-dependent plasticity. One of the most common neurophysiological patterns observed in focal seizures is characterized by low-voltage fast activity at seizure onset, followed by irregular spiking that only subsequently develops into periodic bursting, interspersed with post-burst depressions. This pattern is nearly always seen in human temporal lobe epilepsy [16], in neocortical focal epilepsy, and in acute models of focal seizures. Moreover, there is also a fragmentation of the low amplitude, fast activity, which becomes substituted with a variety of novel background rhythms. Interictal events, additionally, vary in amplitude, pattern, and duration, and are characterized by spikes, sharp waves, and short spike bursts, with rhythmic activity in theta/delta frequency range that can be recorded both within the epileptic zone and around it. In fact, observations of interictal and ictal patterns from epileptic patients showed that synchronization and enhanced excitation were not likely to occur in specific phases of ictogenesis and that synchronous neuronal bursting was not observed during interictal spikes and seizures. Intracranial recordings during the early phase of seizures instead showed that neurons in the epileptic zone and in surrounding areas reduce their firing activity and synchronization, as measured by spiking heterogeneity indices. Transitions into seizure activity due to a localized synchronous enhancement, thus, were relatively rare making them unlikely to contribute to seizure spread. Cumulatively, the data (variability of spiking patterns, the temporal and spatial nonuniformity of foci, and the lack of neighboring recruitment) are therefore caveats to explanations invoking metabolic impairment as a chief vehicle for epileptic globalization, implicating other mechanisms in seizure spreading.

2.3 Globalizing epileptogenesis through higher order cognitive structure: consciousness and the DMN

Unlike the contribution from metabolic impairment, these additional mechanisms likely include interactions with structured cognitive activity [4], including global brain states that govern higher order cognition. Evidence for such influence on two higher order states is considered here, consciousness, and default mode network activity. Both have been shown to be impaired in epilepsy.

2.4 Relating changes in consciousness to epileptogenic spreading

In the most commonly occurring type of chronic, drug-resistant epilepsies, the temporal lobe epilepsies (TLEs), alterations of consciousness (AOC) constitute a particularly dramatic clinical manifestation [17]. Video-EEG recordings reveal that some 60–80% of patients suffering from TLE exhibit AOC during seizures. Due to the frequency of AOC in these patients, the international classification of epileptic seizures has identified impaired consciousness as a framework within which the

main categories of partial seizures, simple and complex, can be differentiated. The association between epilepsy and consciousness, a global, higher order brain state, suggests that specific processes associated with consciousness are factors that may contribute to how epileptogenesis spreads to various brain regions.

Consistent with this, temporal lobe seizures are characterized by epileptic discharges originating from one or several regions of the temporal lobe and propagating through apparently interconnected networks located between cortical and subcortical structures [18]. Among the features that have been shown to contribute to a spreading epileptogenesis during AOC are those involving long-range increases in neural synchrony (as opposed to localized influences of synchronization), that is, between the temporal lobes and regions outside the temporal lobe. Studies of severely affected patients, those exhibiting a complete loss of consciousness, could be distinguished from less severely affected subjects on the basis of synchronization differences seen in long-range measurements. Within the temporal zone, differences during seizures were not markedly different between the two groups but differed significantly when measurements were also made of more distant regions, including the thalamus and parietal cortex. Since the group displaying complete loss of consciousness exhibited a specific increase in synchronization between these widely separated regions, the results suggest that extra-temporal structures are associated with increases in long-range synchrony during AOC [18].

2.5 Changes in default mode network connectivity during epileptogenesis

Another key, higher order structure, the default mode network (DMN), has also been shown to be impaired by epilepsy [8]. The DMN is a major resting network that enables transitioning between task-negative and task-positive states, with functional communication occurring through the basal ganglia. Significantly, several experimental and clinical studies show that the putamen and other BG nuclei are likely to modulate epileptic seizures, with changes in functional connectivity between the DMN and ganglia apparently the source of this modulation. The changes observed in these studies occurred in nuclei of the DMN in epileptic patients even during rest, a task-negative state. Within the DMN, functional connectivity in the left superior, frontal gyrus, left postcentral gyrus, and the right superior temporal gyrus was decreased in epilepsy patients compared with normal controls. Between the basal ganglia and DMN, including the regions belonging to the left lingual gyrus, left and right putamen, right insula/inferior frontal gyrus, and left inferior frontal gyrus, connectivity was increased; that is, the connectivity between the DMN and basal ganglia regions was no longer anticorrelated as in controls, but was instead either insignificant or even slightly positive. Thus, the data suggest that the putamen operates in a manner that is quasi-independent of the DMN during epilepsy, a feature that may relate to changes within nuclei of the DMN itself. Although these studies do not show the emergence of ictal episodes in the DMN, as a group they demonstrate that epileptogenesis can modify functional connectivity in a major neural network at long distances from seizure sites.

3. Mechanisms of neurostimulation: beyond functional inhibition

3.1 Oscillations and spreading regimes in epileptogenesis

The effect of epilepsy on global, higher order cognition suggests that these distributed associations could comprise therapeutic targets. Crucially, neurostimulation has been found to decrease seizure frequency in medically resistant epilepsy,

apparently through mechanisms affecting extended epileptogenic systems [9]. However, details of these mechanisms, like those for motor diseases, remain to be clarified. For example, the proposal of functional inhibition for PD does not explain all functional changes observed in the basal ganglia [19].

Instead of functional inactivation, by mechanisms such as local depolarization block, inactivation of neuronal voltage-dependent channels, or functional deafferentation, functional activation has also been observed in PD. Most of the cells inhibited by high-frequency stimulation still preserve spontaneous activity, for instance. Moreover, tremors in Parkinson's are most prominent during wakefulness, when motions are most frequent, a state characterized as disassociated, but are much reduced in sleep, when down states, which are characterized by associations with large amplitude slow oscillations, are present [4]. These observations indicate that neurostimulation is likely to exert a much more complex influence on neural activity in PD, and, by extension, in epilepsy as well.

The complexity of this influence is likely to be due to several properties known to characterize neural oscillations that are intrinsic to the principle oscillatory patterns seen in normal brain operation [3]. Disease states are known to alter these properties, modifying oscillatory behavior and affecting how neurostimulation can in turn reverse the effects of the disease. The intrinsic ability of oscillators to combine through synchronization, for example, can be evoked via a number of mechanisms such as phase and amplitude coupling [20] and various forms of cross-frequency coupling that configure the conditions for synchrony in which oscillators align and then resonate in unison. Due to their ubiquity throughout the brain they are capable of coordinating with global (proposed to occur through slower oscillations like theta and delta waves), and regional (thought to involve gamma waves) activities [3]. Resonating in unison has the important effect of enabling information transfer and so of regulating communication between brain domains [21]. On the other hand, oscillators must also disengage through desynchronization, where their frequencies are no longer aligned, to generate new combinations with functionally different outcomes. For example, both beta and mu basal ganglia rhythms show event-related desynchronization prior to movement in the basal ganglia, with sustained suppression during movement execution [22]. Desynchronization requires a discrete segregation of oscillator pairs to avoid functional overlap; that is, a qualitative bifurcation of the two that is fundamentally a nonlinear and dynamical event, for which several mechanisms are proposed [21], like phase resetting through pulsing, or noise-induced effects that entrain localized rhythms [20]. Phase shifting, or curve resetting, is a common mechanism for oscillatory control, one already implicated in Wilson Cowan excitatory inhibitory models. By means of spike timing-dependent plasticity, oscillatory phases can be advanced or delayed to adjust synchronization [20], a mechanism that could be evoked by neurostimulation.

Synchronization and desynchronization help the brain to maintain reliability as well as to achieve the flexibility needed for functional variance. Additionally, these "performance" needs must be contextualized in terms of global operation, which ultimately defines the sorts of mechanisms required for the "good" of the whole individual. Significantly, the resident oscillator field is not unimodal, but represents a broad distribution of oscillator attractors elicited by the network connectivity and determined by the physical parameters that give rise to them such as impedance resonance and anatomical configurations [3]. Neurostimulation may drive synchrony with a subset of oscillators but may do so only if the relative coupling between the source of neurostimulation and the neural oscillators is energetically preferred to other combinations, where local instabilities might otherwise disengage them [23].

Critically, for neurostimulation, rigid or full phase locking is rarely if ever achieved [21, 24], a natural physical feature permitting the separation of pair

members with the corresponding potential to form new combinations. Due to the intrinsic tendency for oscillators to align (or disengage), influences of neurostimulation on neural oscillators can be expected to specifically impact the spectral power attained during DBS frequency output, including factors like the extent of phase alignment in the population [20], frequency modulation due to the phase dependency of the coupling constant [21], intermittency of alignment [23], and oscillator disruption that may be occasioned by excessive coupling strength [25]. The need for oscillators to recombine requires that synchronization be of only modest strength. This requirement has led to the current model for oscillator pairing, the Theory of Weakly Coupled Oscillators [3, 21], which is mathematically described by the Adler equation. (Weak here means that interactions lead to phase adjustments without strong perturbations of the oscillatory generative mechanisms.) The Adler equation, accordingly, includes terms for repulsion, termed detuning, and for coupling, both of which vary as a function of the frequency difference between pair members (**Figure 1**).

3.2 Weak associations and neurostimulation

Because perfect synchrony is not strictly attainable, the effect of increasing coupling strength is to increase synchronization residency within a preferred

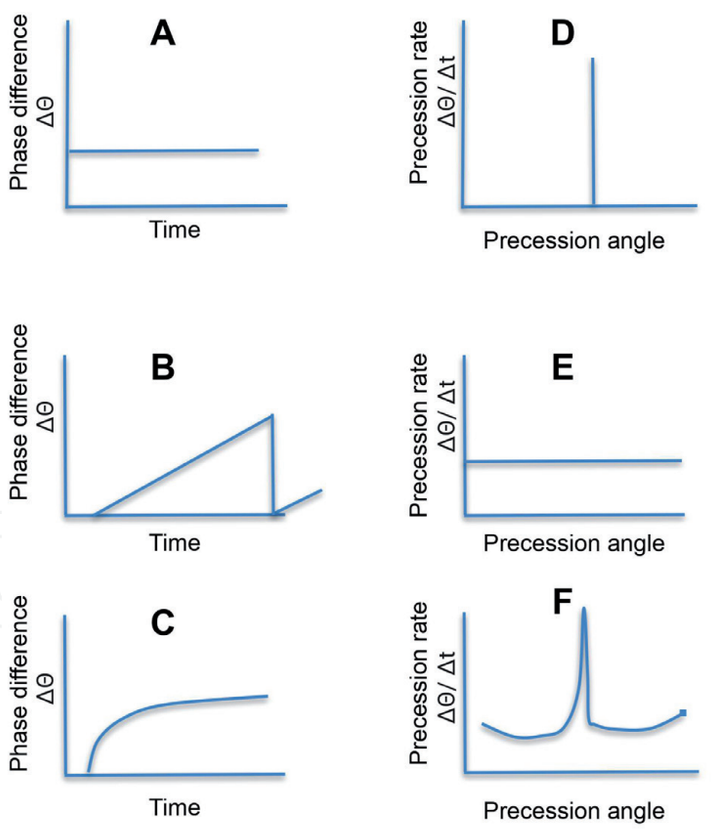

Figure 1.
Synchrony between two oscillators is governed by two factors, the difference between the intrinsic oscillator frequencies and the coupling strength between them. The individual phase evolution for each of two oscillators (A) and (B) is mathematically described: $d\Theta_A/dt = w_A(t)$ and $d\Theta_B/dt = w_B(t)$. From TWCO theory, the evolution of the phase precession angle, Θ_P, is: $d\Theta_P/dt = (w_A(t) - w_B(t)) + Ksin(\Theta_P(t)) + N_P$ (Adler equation). (A and D) Rigid phase locking occurs when the rate of precession equals 0 and the phase difference angle is a constant value. (B and E) The rate of precession is constant and oscillation precesses through all phase angles. (C and F) With coupling, the precession rate is variable and described by the sine of the phase precession angle. Slowing occurs when the phase difference angle is small, termed the phase overlap range, and speed increases when the phase difference is large, a phenomenon known as the Arnold tongue. Such frequency modulation effects result in information transfer in the region of phase overlap [21].

overlap range where oscillator frequency differences are minimal, mathematically described by the sine of the phase angle difference between oscillators. As a result, the oscillators continue to experience frequency modulation throughout the cycle, which is manifest in the continual change in their precession rates (**Figure 1**). (Frequency modulation is posited to lead to information transfer in the maximal overlap range).

Moreover, increasing coupling strength by neurostimulation for the purpose of improving synchronization with a neural oscillator is intrinsically limited and possesses an upper bound [25]. Neural oscillations exhibit stochastic behavior with intermittent synchronization, where neural signals go in and out of synchrony [23] revealing that synchronization (of weakly coupled oscillators) represents a statistical median where a predominant fraction of "micro" oscillating circuits determine the behavior of the population oscillator. Thus, the overall oscillatory distribution may be considered to have a certain phase variance range. Increases in coupling strength, accordingly, can be expected to shift only a proportion of the individual cycling circuits into a non-oscillatory range as increases in the strength of coupling progressively shift the population to a phase lock value near one (**Figure 2**).

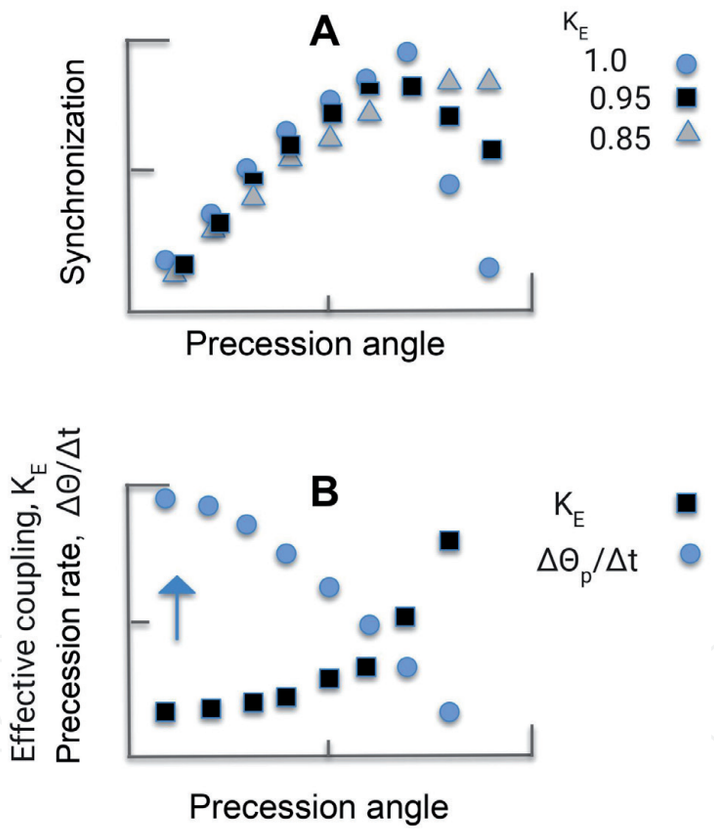

Figure 2.
Effects of varying coupling strength on oscillator attrition. Mathematically, synchronization can be defined in terms of the phase locking value at perfect constancy, that is, equal to 1, minus the influence due to phase precession and the loss of "micro" oscillators due to quenching. Normalized precession influences on synchronization are then described: $S(t) = 1 - d\Theta_P/dt\ (T - t)/d\Theta_P(T) - G((1 - d\Theta_P/dt\ (T - t)/d\Theta_P(T)))$, where $S(t)$ is the relative synchronization as a function t of the precession cycle (T). Ahn and Lubchinsky characterize an oscillating population microstructure [23] in terms of the frequency distribution of the phase differences present within the synchronized set. Using this variance, the proportion of oscillators entering a zone of attrition may then be described by a cumulative normal distribution. Thus only the optimally synchronized set will approach a phase lock value leading to quenching, which is expressed as a product of the cumulative normal distribution and the synchronized population, where G, the fraction entering attrition, can be obtained from the cumulative normal distribution, which is bounded, due to phase variance, at phase constancy. (A) Reduction in synchronization due to oscillator attrition. (B) Variation in the coupling strength constant as a function of the precession angle.

Taken together, the physical properties structuring brain oscillations define a set of parameters within which neurostimulatory intervention could modulate brain dysfunctions.

4. Epileptogenic spreading and neurostimulation affect higher order, global oscillations

Significantly, recent studies demonstrate that epileptic activity affects long-distance oscillatory associations in the brain, including those influencing higher order cognitive activity [26]. A key finding has been the detection of coupling between epileptic electrical activity and slow brain oscillations—posited to mediate interareal coordination of brain activity—in loci distant from seizure origins. Using a biomarker of experimental epileptogenesis, fast ripples (FRs) (high-frequency waveforms that can be induced by kainite injection) the study demonstrated the presence of nonrandom brain activity specifically associated with slow oscillations. Fast ripples were shown to couple with two bandwidths, a slow oscillation in the 3- to 5-Hz range and one involving interictal epileptic episodes in the 20- to 30-Hz range. Phase-amplitude coupling during these events aligned at 4.5 Hz frequency for phase and 27 Hz frequency for amplitude and was 2.1 times higher than during baseline. Domain-specific analyses additionally revealed that the frontal cortex and left and right hippocampi specifically increased in power at 3–5 Hz in all three regions indicating that the ripples were synchronized across these brain domains. Furthermore, the increase in synchronization converged toward a common value, revealing that distribution of phase differences tended to converge and to coincide with the slow oscillation. Additionally, frontal cortex synchronization was delayed with respect to the two hippocampi, demonstrating that functional connectivity was oriented from the hippocampi to the frontal cortices, a finding also confirmed by Grainger analysis. Altogether, the data revealed a strong influence of structured brain activity on epileptogenesis, with cross-frequency coupling between the slow oscillation and FRs shaping the latter's temporal pattern and directionality in the brain.

Critically, epileptic coupling with slow oscillations has been shown to modify memory consolidation, a higher order brain function [27]. Memory consolidation is known to require three patterns of network activity (and their corresponding physiological coupling): hippocampal ripples, neocortical slow oscillations, and neocortical sleep spindles. By selectively eliminating ripples, for instance, memory performance can be greatly impaired in laboratory animals. In normal functioning, the coupling of the three patterns between the hippocampi and prefrontal cortices during NREM sleep leads to consolidation. Experimentally, accordingly, these studies examined how epileptogenesis interfered with the temporal coupling between these events. Specifically, the introduction of experimentally induced, interictal episodes was used to reduce fast ripples. Multivariate correlations between experimentally induced IEDs and fast ripples and spindles then showed that the reduction in FR resulted in significant declines in task-related memory performance, demonstrating a direct effect between the epileptogenic event, the brain patterning, and the inability to recall learned tasks. Significantly, the experimentally induced IEDs modified structured, global activity involving slow oscillations. In all cases, the hippocampal IEDs induced a marked decrease in neuronal firing (relative to baseline firing) within 200 ms, a time window known to be correlated with neuronal hyperpolarization and reduced spiking during NREM sleep and anesthesia that corresponded to slow oscillation, delta waves.

4.1 Neurostimulation treatments

The effects of epilepsy on these higher order oscillatory structures suggest that neurostimulation could restore normal function by reversing these effects. Work in this area remains preliminary, but consistent with this hypothesis.

4.1.1 Vagal nerve stimulation

Therapeutic approaches using neurostimulation for epilepsy primarily involve vagal nerve stimulation (VNS), although other techniques such as deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS) have seen limited use. Existing studies suggest that neurostimulation influences mechanisms of consciousness, which are altered during epilepsy [28]. For afferent vagal nerve fibers, the brainstem nucleus of the solitary tract (NST) is the main relay station. This nucleus has widespread projections to numerous areas in the forebrain, brainstem, thalamus, and areas involved in learning and memory formation (amygdala, hippocampus). Additionally, learning, memory encoding and recall are known to be modulated by arousal, an integral feature of consciousness. Consistent with the observations on the effect of epilepsy on memory consolidation, animal models of vagal nerve stimulation showed that it positively influenced hippocampal long-term potentiation (HLP). In humans, for instance, a chronic increased alertness is observed in VNS-implanted subjects with acute effects on memory consolidation.

4.1.2 DBS

DBS in epilepsy has been applied to a number of targets, including the thalamus (anterior and centromedian nuclei), cerebellum, and basal ganglia (subthalamic nucleus, caudate, substantia nigra pars reticulata). Via the brainstem and basal forebrain arousal systems, the thalamus is hypothesized to underpin consciousness through distributed mechanisms of arousal regulation. Of these, the anterior nucleus of the thalamus appears to underlie limbic seizures and to present in medically resistant seizure formation, whereas the centromedian nucleus of the thalamus is involved in the reticulothalamocortical system that is considered integral to the modulation of vigilance. Significantly, deep brain stimulation of the anterior nucleus of the thalamus has emerged as a promising therapy for drug resistant epilepsy, with recent findings indicating a key mechanistic role for brain oscillations. A study by Chang, for example, showed that desynchronization of the ipsilateral hippocampal background electrical activity over a broad frequency range influenced epileptic discharges, including interictal spikes and high-frequency oscillations [29]. Furthermore, high-frequency stimulation of the anterior nucleus of the thalamus appeared to decouple large-scale neural activity between the hippocampus and regionally distant cortical areas.

5. Summary and conclusion

Singer's discovery in the 1990s of patterned electrical activity for brain communication provided the conceptual basis for moving beyond temporal sequencing for encoded representations [30]. It also overcame the most significant theoretical limitation of Hubel and Wiesel's abstraction thesis for coding, which had been premised on their discovery of motion and edge detector cells in the occipital cortex. The use of rhythmic, typically oscillatory, activity for communication and the ordering of cognition has since been confirmed in a wide variety of studies. This understanding

has enabled a sounder strategy for investigating the structure of brain operation and how the impairment of this structure might lead to brain dysfunction and disease. It has also opened a window to the new therapeutic modes of neuromodulation and neurostimulation. These recent forms of therapy, many described in this volume, are exploiting such understanding to yield the current profusion of medical applications now revolutionizing treatment for brain disease.

Author details

Denis Larrivee[1,2]

1 Loyola University Chicago, USA

2 Mind and Brain Institute, University of Navarra Medical School, Spain

*Address all correspondence to: sallar1@aol.com

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