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NeuroDots: From Single-Target to Brain-Network Modulation: Why and What Is Needed?

Dirk De Ridder, MD, PhD[1]; Muhammad Ali Siddiqi, PhD[2,3,4]; Justin Dauwels, PhD[5]; Wouter A. Serdijn, PhD[3,6]; Christos Strydis, PhD[3,4]

ABSTRACT

Objectives: Current techniques in brain stimulation are still largely based on a phrenologic approach that a single brain target can treat a brain disorder. Nevertheless, meta-analyses of brain implants indicate an overall success rate of 50% improvement in 50% of patients, irrespective of the brain-related disorder. Thus, there is still a large margin for improvement. The goal of this manuscript is to 1) develop a general theoretical framework of brain functioning that is amenable to surgical neuromodulation, and 2) describe the engineering requirements of the next generation of implantable brain stimulators that follow from this theoretic model.

Materials and Methods: A neuroscience and engineering literature review was performed to develop a universal theoretical model of brain functioning and dysfunctioning amenable to surgical neuromodulation.

Results: Even though a single target can modulate an entire network, research in network science reveals that many brain disorders are the consequence of maladaptive interactions among multiple networks rather than a single network. Consequently, targeting the main connector hubs of those multiple interacting networks involved in a brain disorder is theoretically more beneficial. We, thus, envision next-generation network implants that will rely on distributed, multisite neuromodulation targeting correlated and anticorrelated interacting brain networks, juxtaposing alternative implant configurations, and finally providing solid recommendations for the realization of such implants. In doing so, this study pinpoints the potential shortcomings of other similar efforts in the field, which somehow fall short of the requirements.

Conclusion: The concept of network stimulation holds great promise as a universal approach for treating neurologic and psychiatric disorders.

Keywords: Brain, network, neuromodulation, neurostimulation, taxonomy

INTRODUCTION

It has become evident that most brain disorders, whether neurologic or psychiatric in nature, are not the consequence of a phrenologic hyperactivity of one disease-provoking area in the brain but rather emergent properties of altered network activity and connectivity.[1–5]

The normal interactions within and between networks (Fig. 1a) can alter and become pathological, causing brain disorders. These disorder-related networks can be associated with a decrease or increase in existing connections (Fig. 1b), a change in correlated or anticorrelated activity (Fig. 1c), or new connections (Fig. 1d).

Recent advances suggest that neuromodulation-induced changes in broader brain networks are responsible for improvement

Address correspondence to: Dirk De Ridder, MD, PhD, Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin 9054, New Zealand. Email: dirk.deridder@otago.ac.nz

[1] Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand;
[2] Department of Electrical Engineering, Lahore University of Management Sciences, Lahore, Pakistan;
[3] Neuroscience Department, Erasmus Medical Center, Rotterdam, The Netherlands;
[4] Quantum and Computer Engineering Department, Delft University of Technology, Delft, The Netherlands;
[5] Microelectronics Department, Delft University of Technology, Delft, The Netherlands; and
[6] Section Bioelectronics, Delft University of Technology, Delft, The Netherlands

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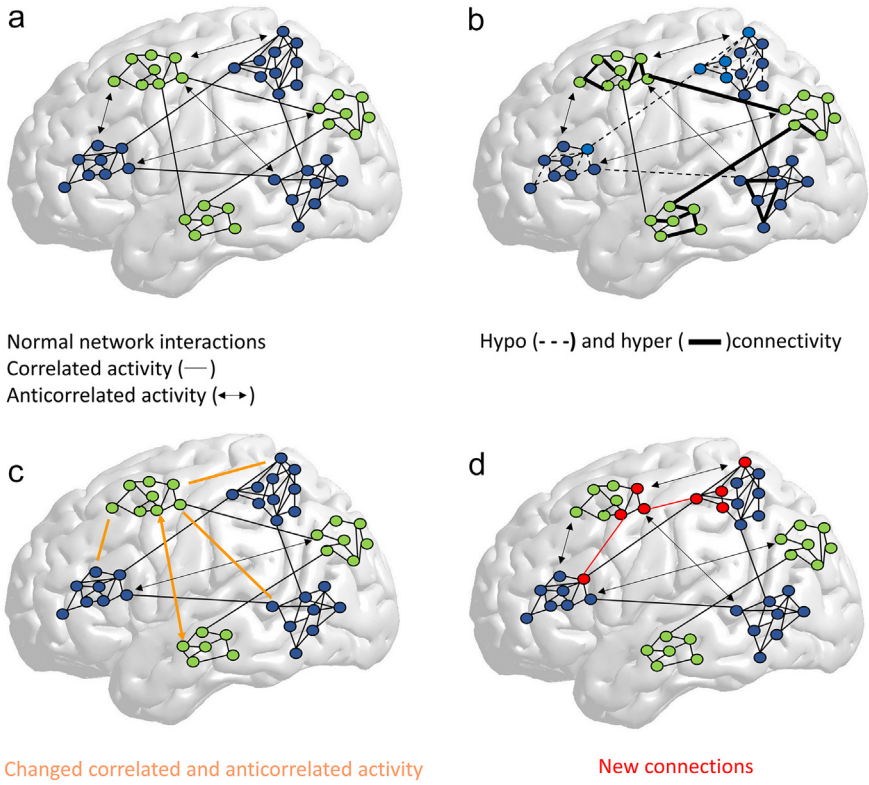


Figure 1. Brain disorders are emergent properties of abnormal connections within or between networks. a. Normal network interactions within and between networks. b. Neurologic and psychiatric disorders may be related to hypo- and hyperactivity of existing connections. c. Neurologic and psychiatric disorders may be related to altered correlated and anticorrelated connectivity. d. Neurologic and psychiatric disorders may be related to new connections. [Color figure can be viewed at www.neuromodulationjournal.org]

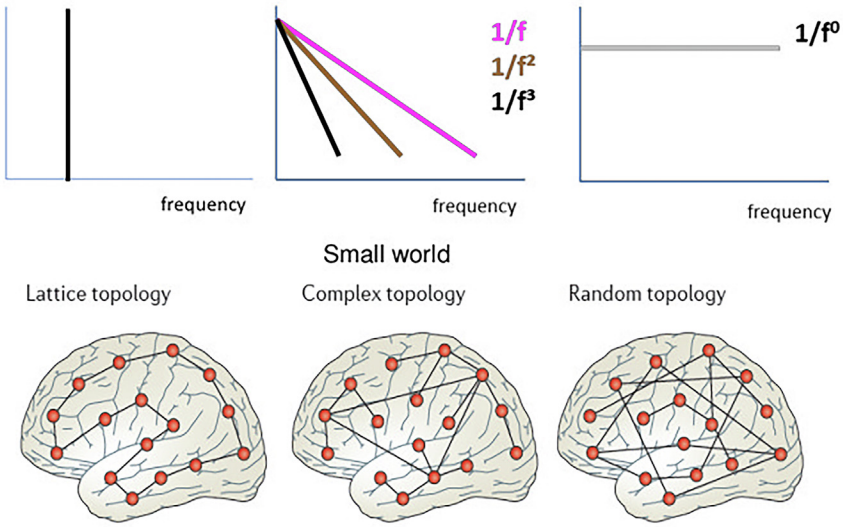
of neuropsychiatric symptoms, rather than local impact at the stimulation site.[6–8] Such a connectomic neuromodulation approach requires a shift from phrenologic thinking to network and interacting network considerations.

The intention of this manuscript is to create a theoretical framework for developing greatly needed, next-generation brain implants that shift from the current phrenologic single-area target to "network neuromodulators". The manuscript comprises four sections. The first section explains the pressing need for these novel devices from a clinical standpoint, in addition to the pathophysiological mechanisms common to most brain disorders, based on an emergentist and monist philosophy in the setting of considering the brain as a complex adaptive system. The technical requirements of such devices are specified in the next sections, without going too much into details for which there exist specialized journals. We acknowledge that an interdisciplinary neurosurgery/neuroscience/engineering manuscript may have some information only relevant for neurosurgical neuromodulators and some information only relevant for engineers. Reducing it by removing most of the already limited technical information risks turning the manuscript into a "science fiction" rather than "science faction" approach, ie, a manuscript that the readers either believe or not. By consolidating the minimal engineering achievements already available or needing to be developed, it becomes evident for the reader that, in principle, network neuromodulation is feasible.

This manuscript, then, identifies the principles that these network neuromodulators must obey to be innovative and clinically applicable. Having laid this foundation, the next step will be the design and prototyping of the optimal network neuromodulator. The authors have not yet developed or even started developing a prototype of this network neuromodulator but want to propose a theoretical network-science–based foundation as a template or basis to guide this development attempt.

WHY SHIFT FROM SINGLE-AREA TO NETWORK NEUROMODULATION?

Psychosurgery, meaning the application of surgical lesions in the brain, was developed in the 1930s in an attempt to develop a more humane treatment for psychiatric disorders than being locked away for the rest of one's life in overcrowded and underfunded asylums.[9] Intriguingly, the outcome in hundreds of thousands of patients who underwent this form of treatment converged on a rule of three: One-third of patients experienced marked improvement; one-third experienced no or slight improvement, and one-third experienced no change or worsening of their condition.[9–11] Once medication was discovered that could treat psychiatric disorders, it largely replaced psychosurgery, but since 2010, a steady decline of pharmaceutical interest in developing neuropharmacologic products has been noticed, whether for neurologic or psychiatric indications. The reason is that developing medication for the central nervous system has 50% less chance of making it to the market (6.2% vs 13.3%), takes 30% longer (19.3 vs 14.7 months), and costs 30% more than heart medication.[12] Consequently, large pharmaceutical companies have lost interest in neuroscience, causing a 50% decrease in investment for brain-related diseases.[13]



	Regular Lattice	Small World Complex brain	Random
adaptive	determined	flexible	completely free
Shortest path length	High	Small	Small
Clustering coefficient	High	High	Small

Figure 2. The brain as a complex adaptive system has an intermediate topology between two extremes: the regular or lattice topology and the random topology, each with different characteristics. [Color figure can be viewed at www.neuromodulationjournal.org]

Neuromodulation can fill this therapeutic gap, but that requires a whole new breed of devices. To illustrate, even though deep-brain stimulation (DBS) is heralded as being highly successful, its success is relative: Meta-analyses that evaluate the outcome of brain stimulation through implanted devices yield 50% success rate, meaning 50% improvement in 50% of patients after five years. This holds for every brain disorder for which implants are provided, be it depression,[14] pain,[15] tinnitus,[16] obsessive compulsive disorder (OCD),[17] dystonia,[18] Parkinson's disease,[19] etc. Furthermore, if outcome measures are recorded in a nonbinary way (of responders versus nonresponders) but in a way that allows three outcomes, this produces one-third major improvement, one-third somewhat improvement, and one-third not improved or worse, similar to outcomes noted in psychosurgery. Thus, there is a large margin for improvement. In the setting of Parkinson's disease, for example, it has been argued that these unsatisfactory long-term results are not to be seen as failures of the DBS procedure per se but result from further progression of a degenerative disease. Nevertheless, this argument is unconvincing because outcomes in pain, tinnitus, major depression, etc, are similar, and these disorders have not been considered as degenerative brain pathologies.

From a biological standpoint, the brain evolved to reduce the inherent uncertainty present in a changing environment,[20] especially once living creatures started moving around.[21] The brain can be seen as a Helmholtzian prediction machine,[22,23] actively sampling the internal and external environment for information to update its predictions in a Bayesian way.[20,24]

From an engineering standpoint, the brain is a complex adaptive system,[25,26] analogous to the internet, an ant colony, the economy, or a social-relations network. A complex adaptive system can be interchangeably used with the term complex dynamic system and, in the setting of the brain, with the term complex neuroplastic system.

A complex adaptive system has an intermediate topology between two extremes, a lattice or regular topology and a random topology[27] (Fig. 2). Both extremes are not compatible with conscious brain states and are not adaptive: A lattice topology is fully determined, and a random topology is completely free. A complex adaptive system has a small world topology[28,29] and

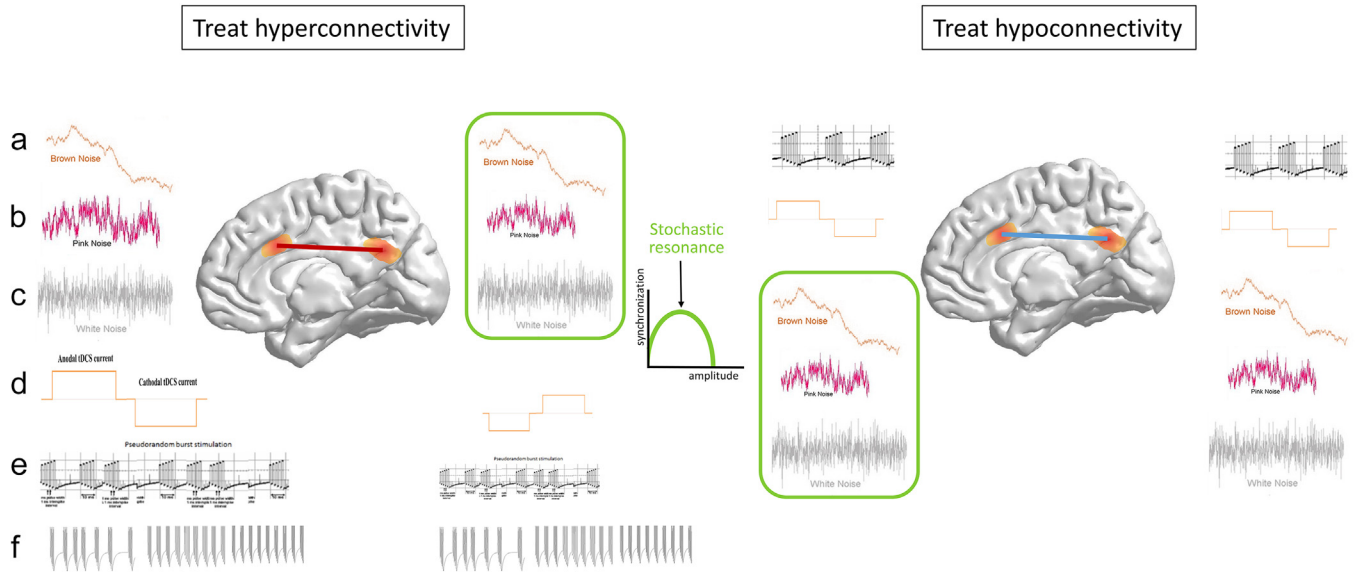


Figure 3. Treating hyper- and hypo-connectivity in the brain with different stimulation designs. a. Brown noise. b. Pink noise. c. White noise. d. Low-frequency stimulation in antiphase. e. Pseudorandom burst stimulation. f. Infraslow in-phase stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

is characterized by adaptive flexibility, ie, is amenable to neuromodulation.

For the brain to qualify as a complex adaptive system, it must fulfill two criteria.[30] It requires a structure following a "small-world topology," and it must embed noise.[30] These two characteristics permit a system to be adaptive and flexible. The brain is noisy, but the noise is structured, generally following a $1/f$ or $1/f^2$ power-law distribution.[31–34] The $1/f$ structure implies that a network has memory and can carry information, in contrast to white noise, which reflects pure randomness[35] (Fig. 2). A system with a power-law distribution can learn while still maintaining stability. All complex adaptive systems share the same characteristics, one of which is "emergence," meaning that the whole is more than the sum of its components. From its individual components, the combined network properties cannot be predicted; the properties emerge. Thus, emergence is a process whereby larger entities, patterns, and regularities arise through interactions among smaller or simpler entities that themselves do not exhibit such properties. All constituent parts of a car do not make a car, unless they are connected in a very specific way for a functional car to emerge.[36] Of course, a standard car is not adaptive; it is a complex system but not adaptive. In complex adaptive systems like the brain, not every adaptation is beneficial, while maladaptive changes can lead to neurologic or psychiatric disorders by maladaptive activity and connectivity changes.[2]

On the basis of this concept, many brain disorders have indeed been regarded as connectivity problems,[1–5] and consequently, network science has been embraced as a novel approach for studying brain disorders.[29,37–39] Connectivity in a complex adaptive system exists at an anatomical level, called *structural* connectivity, and at a functional level, called *functional and effective* (ie, directional functional) connectivity.[40] Structural connectivity refers to the presence of anatomical, biological-fiber pathways in the nervous system, which are relatively static at shorter time scales (seconds to minutes) but can be dynamic at longer time scales (hours to days) during learning or development.[40] Thus, even anatomical connections are not hardwired but change with experience or deprivation thereof. Functional connectivity is fundamentally a statistical and not an anatomical concept, looking at patterns of correlated activity between different brain areas by measuring frequency or phase.[40] In contrast to structural connectivity, which is based on hardwired anatomical white-matter tracts, functional connectivity changes constantly, by instantaneously adjusting correlated activity to endogenous or exogenous stimuli. Another form of functional connectivity computes cross-frequency coupling between different oscillatory frequencies, in which higher oscillations (β and γ) are nested hierarchically[41] on slower oscillatory frequencies (infraslow, slow, Δ, θ and α), which act as carrier waves. Functional connectivity does not assume any directional flow of information. This is implicitly calculated by effective connectivity, which computes the origin and destination of information flow in the brain. Effective connectivity can, therefore, be considered directional, functional connectivity and is often based on time series, in which the underlying idea is that causes predate effects. Structural, functional, and effective connectivity are all related to each other.

Functional connectivity is the basis of multiple separable brain networks, yet these brain networks are not all active at the same time. When one network is activated, others may be inactive or less active, producing anticorrelated activity among these networks.[42] Some separable networks may be coactivated, leading to correlated activity. This has led to the development of the triple network model, which is a network-science–based approach explaining core interactions in multiple cognitive and affective disorders.[43] It states that neurologic and psychiatric disorders are the result of aberrant interactions within and among three canonical brain networks. These three networks include the self-representational default mode network,[44,45] the behavioral relevance encoding salience network,[46] and the goal-oriented frontoparietal central executive network.[46,47] Normally, the salience network and the central executive network are characterized by correlated activity, and both networks are anticorrelated to the default mode network.[42] The salience network acts as a switch between the anticorrelated default mode network

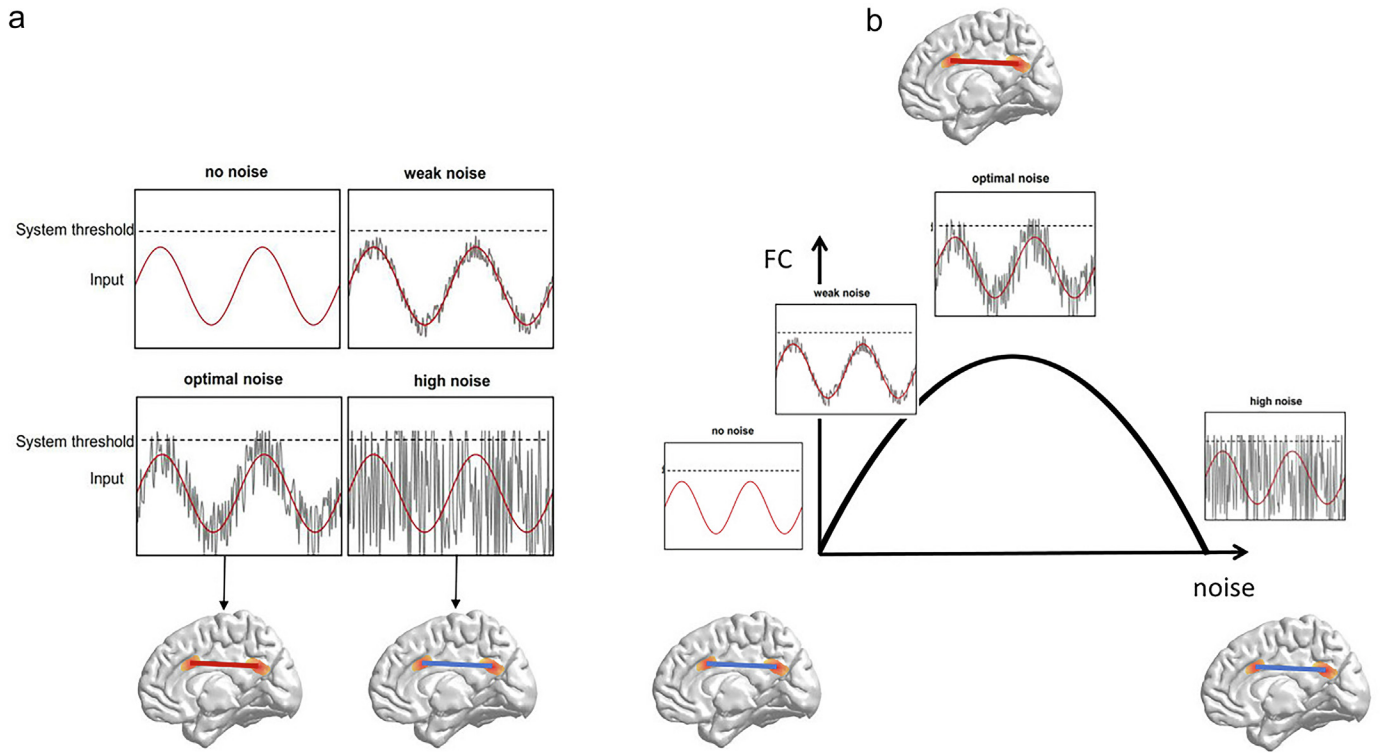


Figure 4. Stochastic-resonance effect of noise stimulation can both increase and decrease connectivity. With low amplitudes, no change in connectivity ensues because the firing threshold is not reached (weak noise in panel a). Optimal amplitudes push activity at different areas above threshold, leading to increased connectivity (optimal noise, panel b). High amplitudes create noise at the two areas, preventing phase synchronization and thus functional connectivity (high noise, panel a). This creates an inverted U-curve profile in connectivity (panel b). FC, functional connectivity. [Color figure can be viewed at www.neuromodulationjournal.org]

and the central executive network.[48,49] This is in keeping with the proposed functions of the three networks. When the salience network identifies a behaviorally relevant event in the environment, it reduces the activity of the self-oriented and mind-wandering default mode network and activates the external goal-oriented central executive network to deal with the external salient event.

Functional and effective connectivity is constrained by the presence of both direct and indirect anatomical connections, and correlated activity can change structural connectivity through Hebbian mechanisms (cells that fire together wire together).[50] These dynamical changes in structural, functional, and effective connectivity are the basis of the concept of neuroplasticity and are crucial to developing novel devices that can not only break pathological connections but also rebuild normal physiological connections. It has been proposed that this requires two different stimulation designs, one that can optimally strengthen connectivity, such as burst-like stimulation, and one that can break functional connections, such as noise-like stimulation.[36,51] Hyperconnectivity can be treated by surgically severing the connection or electrophysiologically via noise stimulation, low-frequency stimulation in antiphase, or pseudorandom burst stimulation[36] (Fig. 3, left). Hypoconnectivity, in contrast, can be treated by burst stimulation in two targets in synchrony, by infraslow in-phase stimulation and by noise stimulation (Fig. 3, right).[36] Noise stimulation can thus both break and build connectivity through a stochastic-resonance effect (Fig. 4).

Multiple brain disorders exhibit similar changes in network activity and connectivity. These common pathophysiological mechanisms can be genetic, physiological, and anatomical.

The same risk genes may cause multiple different neurologic and psychiatric disorders, known as pleiotropy.[52–56] Depending on the environment, the same risk genes may change functional connectivity by modulating epigenetic gene expression in the brain,[54] causing different emergent properties, that is, different neurologic and psychiatric disorders. For example, genetic overlap exists in the reward deficiency syndrome, a group of disorders encompassing addictions (substance and nonsubstance), impulsivity, obsessive compulsive disorder (OCD), and personality disorders with a common underlying mechanism.[57,58]

Electrophysiologically, the entity called thalamocortical dysrhythmia groups pain, tinnitus, Parkinson's disease, depression, and slow-wave epilepsy,[59] and is characterized by a common core of β activity in the dorsal anterior cingulate cortex and the parahippocampus, and θ–γ or θ–β cross-frequency coupling in the respective motor or sensory cortex distinguishing the separate clinical entities.[60]

Furthermore, many psychiatric disorders (schizophrenia, bipolar disorder, depression, addiction, OCD, anxiety) share a common anatomical substrate. The salience-network dysfunction is at the core of these disorders.[61] Since the salience network, which is atrophic in many psychiatric disorders, is dysfunctional, its function as a switch between internally directed cognition of the default mode network and externally directed cognition of the central executive network is disrupted. This leads to abnormal functional connectivity within and among these three networks as expressed by correlated and anticorrelated activity within and among the three cardinal networks. And indeed, common or shared hypo- and hyperconnectivity changes are identified in numerous brain

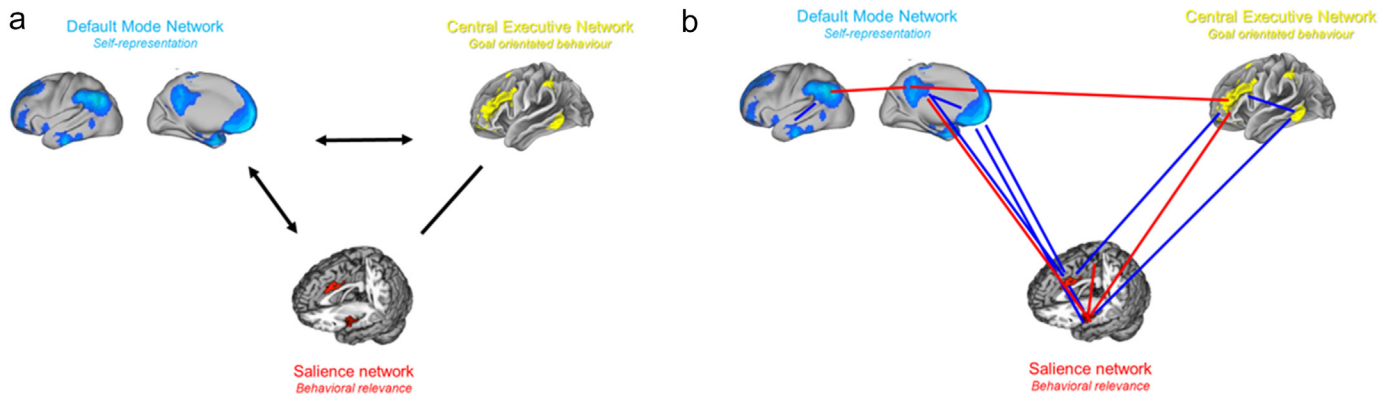


Figure 5. ADHD, anxiety, depression, bipolar, autism, OCD, PTSD, and schizophrenia are characterized by common connectivity changes that could be primary targets for normalization. a) Normal interactions. b) Abnormal interactions: red lines = increased functional connectivity, blue lines = decreased functional connectivity, based on meta-analysis.[5] [Color figure can be viewed at www.neuromodulationjournal.org]

disorders, including attention-deficit hyperactivity disorder (ADHD), anxiety, depression, bipolar disorder, autism, OCD, posttraumatic stress disorder (PTSD), and schizophrenia[4,5] (Fig. 5). This meta-analysis of the aforementioned neuropsychiatric disorders indicates that they are all characterized by the default-mode network and salience network falling apart and becoming dysfunctionally (maladaptively) reconnected with other networks, for example, correlated between salience and default mode instead of anti-correlated, producing different emergent properties of the newly formed networks, that is, the neuropsychiatric disorder. This finding suggests that a universal treatment should restore the intranetwork connectivity of the default mode and salience network, in addition to the internetwork connectivity.

These anatomical and physiological shared mechanisms should permit the development of universal brain network neuromodulators that target the common pathophysiological mechanisms of these pathologies, rather than developing a dedicated device for each disorder individually.

Using network science, which studies complex adaptive systems, it has been shown that random attacks on (brain) networks are not capable of disrupting a network[62] and thus also not eliminating the emergent property of the network.[63] Therefore, a targeted attack[62] on the main hubs of the network or multiple interacting networks[43,64] that are involved in the brain disorder is more likely to exert a beneficial effect.[63] This agrees with a meta-analysis on DBS for pain, which shows that multitarget implants yield better outcomes than does single-target stimulation, especially if both lateral and descending pain-inhibitory pathways are jointly targeted.[15] Similarly, multitarget modulation also seems more beneficial for tinnitus than single-target stimulation, both noninvasively[65–67] and invasively.[68]

This multitarget approach has been extended to treatment-resistant depression.[69] After initial surgery comprising intracranially implanting four DBS leads (bilateral subcallosal cortex and ventral striatum) and ten stereoelectroencephalogram electrodes in downstream depression-relevant frontotemporal network regions (bilateral dorsolateral prefrontal cortex, ventrolateral and ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and mesial temporal lobe), the patient was stimulated on the two sites, that is, both the subcallosal cortex and ventral striatum, given single-target stimulation of the sucallosal cortex without ventral striatum worsened the clinical results. Importantly, the stimulation parameter settings were informed by the data obtained from the temporarily implanted ten stereoelectroencephalogram electrodes, which picked up changes induced by the stimulation on the four stimulation electrodes,[69] indicating the feasibility and benefit of a network approach.

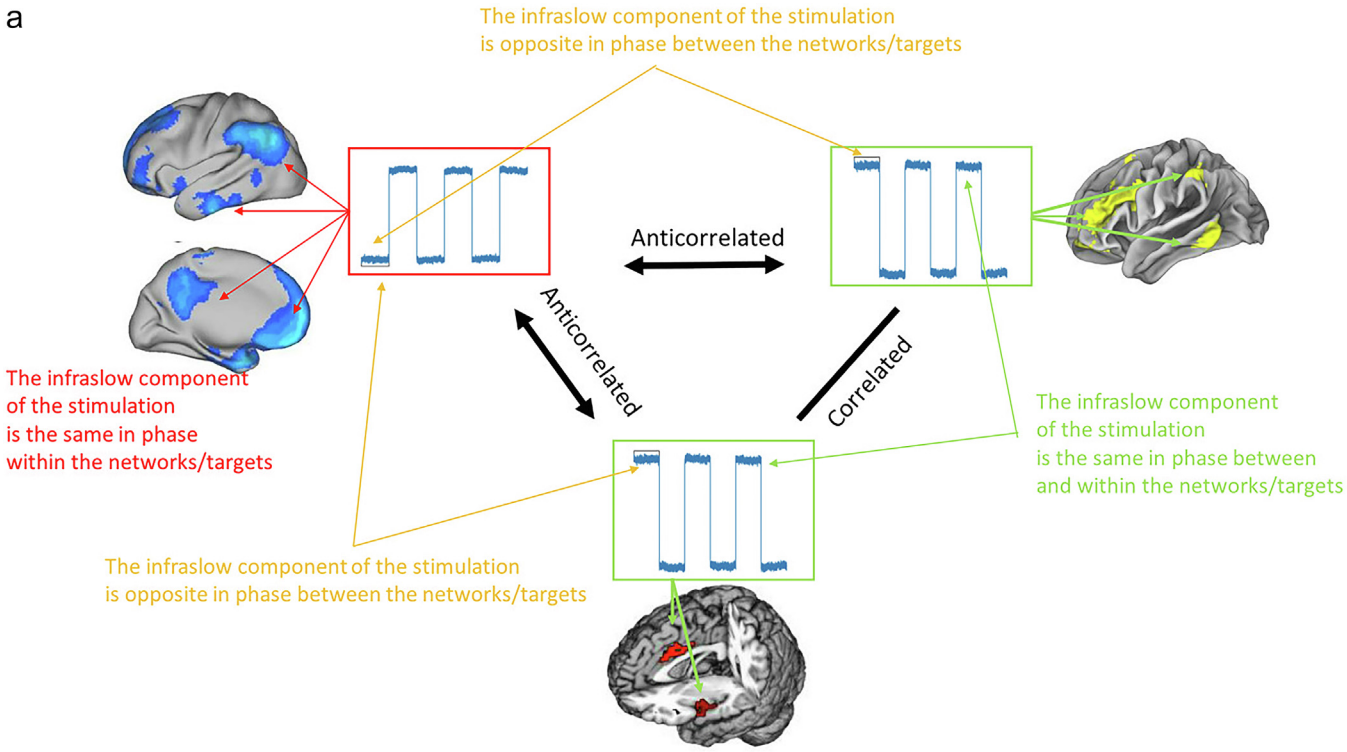
It has further been shown in a small case series that the delivered stimulation also can be informed and refined by time-based adaptation of stimulation control, adjusting stimulation to patient-specific biological rhythms, as an adjunct to classical control methods.[70] This leads to the suggestion that to optimize patient-specific therapeutic outcomes, the neuromodulation device needs to incorporate feedforward, feedback, and adaptive control strategies together to maximize therapeutic benefits for patients and provide more natural regulation of patient pathophysiology to restore healthy physiological homeostasis.[70]

Nevertheless, one also can attempt to start with targeting common connectivity abnormalities shared by multiple different brain disorders. An example is to develop triple network neuromodulation to treat ADHD, anxiety, depression, bipolar, autism, OCD, PTSD, or schizophrenia would involve sensing correlated activity within each of the three canonical networks, in addition to among the three networks. If an abnormal infraslow phase synchronization is detected among some nodes, the nodes need to adjust their activity so that the intranetwork phase synchrony is restored but also in such a way that the internetwork infraslow phase synchronies are restored to normal correlated activity between salience network and central executive network, and anticorrelated between these two networks and the default mode network. This cannot be achieved by single-target or even dual-target stimulation but requires the integrated activity of multiple widely distributed stimulators that can sense, communicate, and stimulate in an adaptive and flexible way, as shown in Fig. 6a.

Transcranial electrical stimulation devices capable of normalizing the triple network interactions through applying anticorrelated and correlated activity are already commercially available. One such device has 32 independently controlled channels that can deliver fractionated currents of choice (tonic, burst, infraslow, pink noise, blue noise, gray noise, or a combination of currents) (Starstim, Neuroelectrics, Barcelona, Spain) (Fig. 6b).

This allows use of the infraslow component (0.1 Hz) to correlate activity within a network and between networks that are normally correlated, such as the salience network and central executive network, by synchronizing the phase of the infraslow component among the nodes of each network or between the networks

a

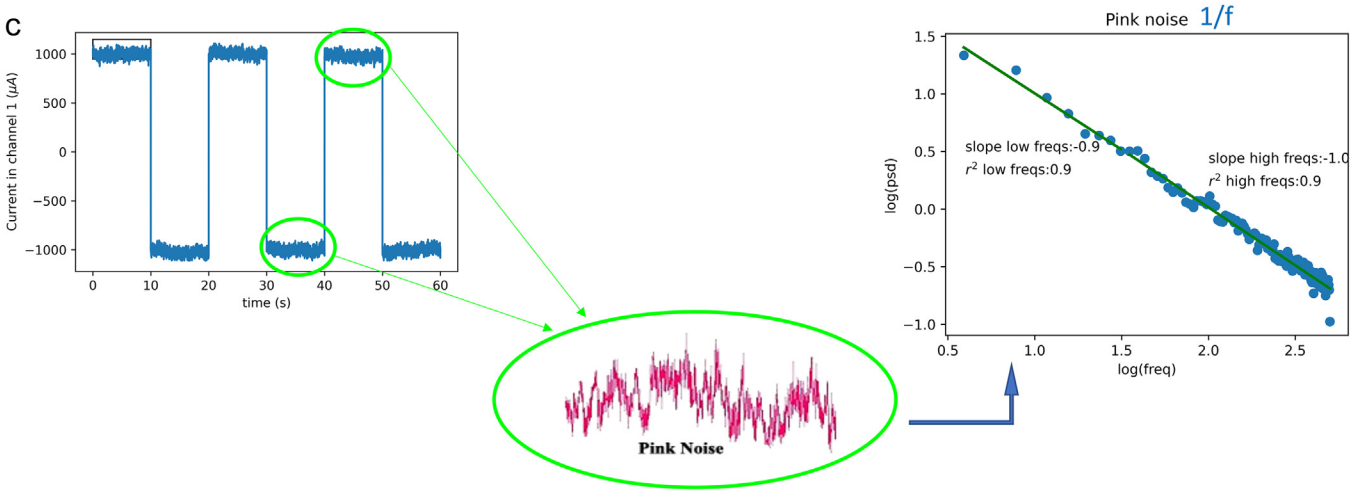


b

Stimulation functionality

Number of channels: (up to) 32
Sampling rate: 1000 SPS
Stimulation types: tDCS, tACS and tRNS
Customized waveform
Frequency range: 0-250 Hz (tACS): 0-500 Hz (tRNS)
Configurable bandpass filter for tRNS
Maximum current per channel: ± 2mA
Current accuracy: 1%
Current resolution: 1 μA
Current is configurable independently for each channel
Configurable Ramp-up and Ramp-down times
Voltage: ± 15 V per electrode (30 V potential difference)
Sham and Double blind modes available
Operating time: Wifi: 3h 30 min, USB: 4h 50 min

Figure 6. Non-invasive transcranial infraslow stimulation with nested pink noise. a. This panel illustrates normalization of triple network interactions through infraslow stimulation combined with pink noise nested on top of the infraslow stimulus. The infraslow component permits correlation of activity within networks and between the salience and central executive network. It also permits anticorrelation of activity between the default mode and the salience and central executive network by supplying infraslow stimuli in antiphase at the default mode and the salience plus central executive network. The pink noise nested on top of this infraslow component serves to mimic normal physiologic brain activity. b. This panel presents a multichannel transcranial electrical stimulation device, in which each of the different channels can be independently controlled, permitting fractionated stimulation of multiple different stimulation designs. c. This panel illustrates pink noise stimulation nested on an infraslow component. d. This panel presents a computer simulation of the fractionated current flow of the infraslow and pink noise component for normalizing the triple network, as developed by Neuroelectrics. SPS, samples per second; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tRNS, transcranial random noise stimulation; USB, universal serial bus. [Color figure can be viewed at www.neuromodulationjournal.org]



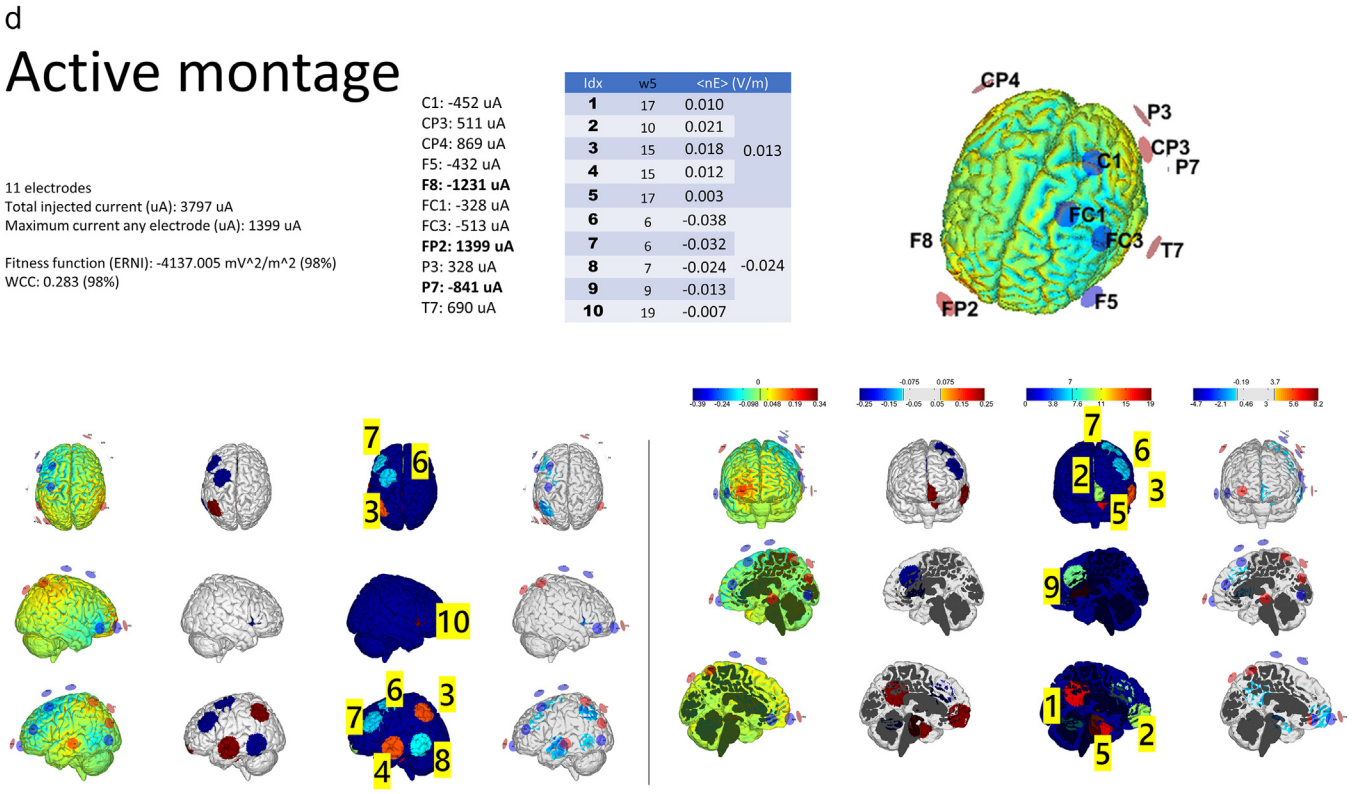


Figure 6. (*continued*). [Color figure can be viewed at www.neuromodulationjournal.org]

requiring resynchronization. By delivering opposite phases of the 0.1 Hz among networks that need to be anticorrelated, for example, the default mode network is anticorrelated to the salience network and the central executive network, this anticorrelated activity can be reintroduced. Furthermore, by nesting pink or brown noise on top of the correlated or anticorrelated activity, mimicking of physiological power law activity[31,71] can be achieved. This is visually presented in Figure 6c.

As such, from a theoretical perspective, this approach could represent a universally applicable approach to normalize abnormal connectivity within and between brain networks. A first yet unpublished clinical study applying this complex triple network normalization approach suggests it is feasible and significantly improves internalizing disorders. In that study, the goal is to normalize the left central executive network and left default mode and right salience network. We selected a lateralized approach to limit the number of brain areas to be targeted, and since the canonical brain networks that form the triple network are lateralized (default mode and central executive to the left, salience to the right[72–74]).

The computation of fractionation of the delivered current and current type is performed by mathematical simulations that use a standard head model, in addition to a neurosynth-based (www.neurosynth.org) meta-analytic approach to delineate the normal physiological functional connectivity that can be used to carry the current to deeper structures.[8,75,76] An example of the computer

simulation for the fractionated current delivery to normalize the triple network is presented in Figure 6d.

A NEW PARADIGM: NEURODOTS

On the basis of the previously mentioned theoretical and clinical arguments, it seems evident that a new breed of network neuromodulation devices—henceforth, we collectively term them NeuroDots—is greatly needed, if the field of clinical neuromodulation is to move to a new era of more successful treatment, irrespective of the brain disorder under study or treatment. The NeuroDots will have to incorporate a set of criteria, both for hardware and software, that will permit normalization of pathological activity and connectivity. In summary, multiple independent stimulating and recording devices, called NeuroDots, interact with each other (like ants in an ant colony) to deliver an adaptive set of synchronizing and/or desynchronizing stimuli, based on sensed data that measure activity and connectivity. The NeuroDots all connect to a central control system through a cranial implant. In the later sections, we proceed to outline an initial list of clinical and technical requirements to that effect.

An overview of NeuroDots is presented in Figure 7, which depicts the way the different networked implantable devices are connected to the clinician by means of a portable device; more details are provided in a later section. We envision the NeuroDots nodes to be designed in such a way that they will be sufficiently powerful and diverse in function, ideally only requiring software updates, like apps on a smartphone, to target different brain disorders. Such a generic-design approach has already been shown to be possible for traditional implantable devices, eg, pacemakers.[77]

NEURODOTS CLINICAL REQUIREMENTS

The requirements for NeuroDots implants from a clinical standpoint are described below:

1. Multisite: Multiple, independently controllable but communicating, small ("dot") devices can sense activity (local-field potentials) and connectivity with high resolution, ie, frequency, amplitude, and phase relationships among the different NeuroDots implants. Depending on the application, the dot devices also will be able to stimulate multiple sites. In this work, dot nodes/implants refer to all subdural implants, eg, cortical implants for brain-computer interfaces or deeper implants for DBS.
2. Multifunction: Dot devices can individually and as a network provide multiple stimulation designs that can restore connectivity (eg, synchronous burst, infraslow in phase, stochastic noise) or break connectivity (eg, asynchronous burst, antiphase infraslow, or high amplitude noise) (Fig. 3).
3. Highly autonomous: The dot devices adjust their flexible output on the basis of what is sensed, in a closed-loop fashion, without human intervention or constant monitoring.

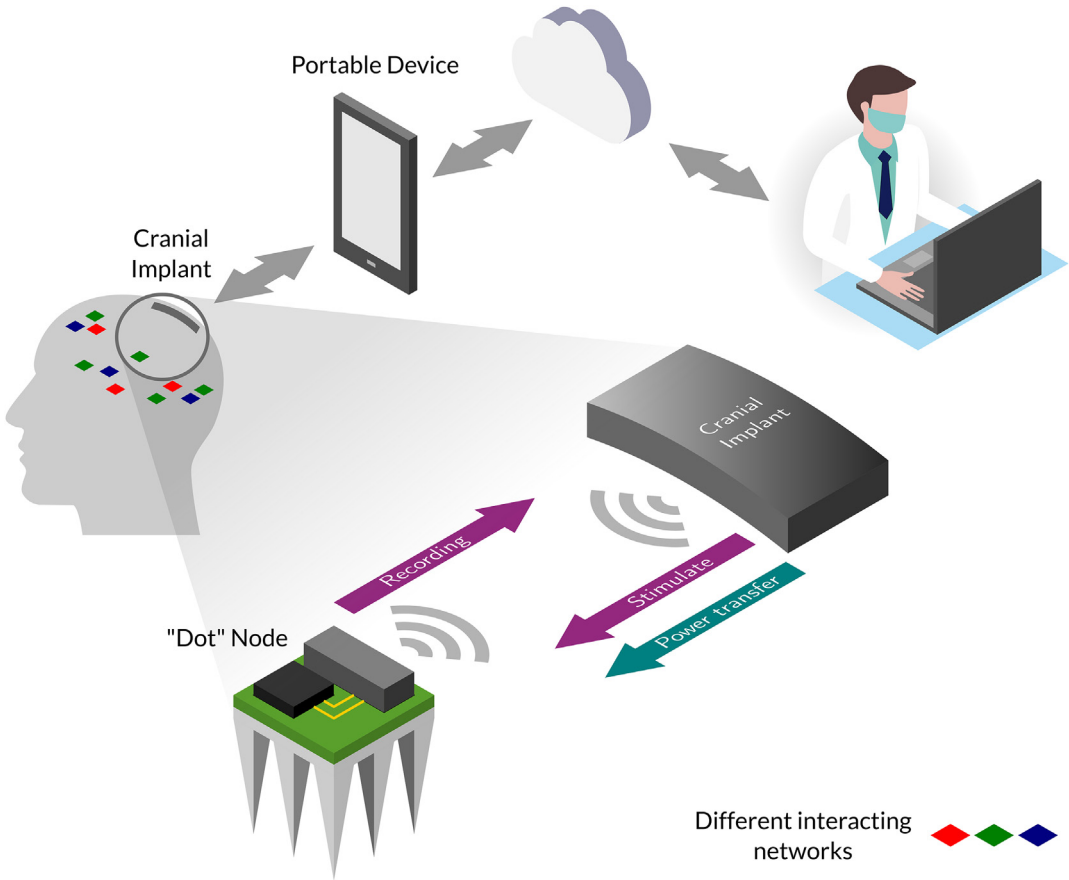


Figure 7. NeuroDots concept: Multiple independent stimulating and recording devices interact with each other to deliver an adaptive set of synchronizing or desynchronizing stimuli, based on sensed data that measure activity and connectivity. The NeuroDots all connect to a central control system through a cranial implant. [Color figure can be viewed at www.neuromodulationjournal.org]

4. In vivo reprogrammable: NeuroDots operation is upgradable on site and in vivo, through software updates.
5. Data logging: The NeuroDots system can store sufficiently large amounts of operational data to facilitate advanced data analysis, patient diagnosis, and treatment.
6. Generic in use: The NeuroDots system is flexible enough for the implants to be inserted in any desired anatomical target of a pathological brain network, in such a way that it can address different neurologic problems.
7. Minimally invasive: The NeuroDots system is as minimally invasive as possible for achieving high user acceptability and low tissue damage. We acknowledge that the safety profile of the implants is very important; implanting an individual NeuroDot does not increase the risk profile to current single-target implants. However, many NeuroDots need to be implanted, which might lead to an increased risk by summating the low risk of each individual implant. Nevertheless, this contemplation has not prevented other devices, such as Neuralink, from receiving approval for human studies, and in this device, 64 threads are inserted per link, producing a higher cumulated risk profile than that of the proposed Neurodots. Thus, the institutional review board and ethical committee must have considered that the potential benefits outweigh the risks. Furthermore, in epilepsy surgery and more recently also in deep brain surgery for depression, many stereotactic leads are implanted to discover either the focus of the epilepsy or to study the effects of stimulation activation.[69] On average, between ten and 15 electrodes are implanted,[78] with a hematoma risk of <1% (0.8%), as shown by a meta-analysis with 33,000 electrodes.[79] Furthermore, it is evident that once developed, the NeuroDot technology will first be tested in animals to indicate its safety profile and feasibility. The risk of migration of the implanted devices is similar to that of other single-target devices such as neural dust,[80,81] in addition to methods to implant and retrieve potentially dysfunctional NeuroDots, using magnetic steering[82,83] or endovascular delivery of the NeuroDots. Although the endovascular approach is intuitively appealing, in its current form, the stentrode,[84,85] it is restricted to the large blood vessels such as the superior sagittal sinus. When the treating neurosurgeon/neuromodulator wants to target multiple networks, certainly this can be considered in some nodes that are near a large blood vessel. However, in small arterial or venous branches, this may cause blood flow restrictions, with a stroke as a result. Thus, a hybrid approach is conceivable in which stentrodes are combined with intracranial electrodes.
8. Chronic operation: The NeuroDots system can function for a very long time (>ten years).
9. Biocompatible: The NeuroDots components are compatible with the neighboring brain tissue.
10. Ecological: Safe and reliable implantation, explantation, and operation of NeuroDots components are essential.

NEURODOTS TECHNICAL REQUIREMENTS

The previous list of clinical requirements elicits several necessary technical requirements that must be satisfied, as follows:

1. Large coverage: Given the brain is a complex adaptive system, the neuromodulation device either needs to span a large area or volume of the brain or it must be subdivided into multiple distributed dot implants that are connected in a wired fashion or wirelessly, all operating with a chosen degree of autonomy, an aspect that we will discuss later.
2. High elasticity and biostability: NeuroDots implants will be elastic, of similar elasticity to that of the tissue in which they are implanted. This is measured by the Young modulus. Because brain matter is extremely soft—as indicated by its small Young's modulus of only approximately 1.5 kPa—brain implants for neuromodulation also should ideally be soft, bendable, flexible, and stretchable. The implants must be able to move along with the movements of the brain and follow its curvature, the lobes with its gyri, sulci, and fissures. This is in stark contrast to the bulky and rigid implants that we have today, with Young's moduli of approximately 150 GPa, which is, eg, eight orders of magnitude greater/stiffer than brain matter.[86] Moreover, the electrodes that interface the electronics with the ionics of the brain are usually organized in one-dimensional arrays, with ring or semiring electrodes, or in planar (two-dimensional) arrays, and thus limited in the volume that they can cover. The distribution of the NeuroDots functionality over multiple dot implants can alleviate this volumetric requirement to a certain extent but imposes other challenges, as will be addressed later.
3. Efficacious neuromodulation: Efficacious neuromodulation will be delivered by dot implants, which interact with neurons and glia by modulating their tendency to generate action potentials and thus can have an excitatory effect or an inhibitory effect on the neurons to which they are connected. The simplest approach is electrical stimulation, but other forms of neuronal and glial modulation can be achieved by magnetic, light, or ultrasound stimulation.[87]

   Electrical stimulation requires the electrodes to be close to the neuromodulation site. Moreover, it requires a direct electrical contact between the electronics of the implant and the ionics of the tissue, which places constraints on the encapsulation of the neuromodulation devices. Unlike electricity, magnetism-based neuromodulation does not require a direct contact but still close vicinity to the neuromodulation site. Neuromodulation by means of light, often referred to as optogenetic neuromodulation, is a biological technique that uses the expression of light-sensitive ion channels, pumps, or enzymes in the neurons. Optogenetics requires delivering genes that encode proteins capable of conveying light sensitivity to neurons.[88,89] Owing to the limited optical transparency of the brain, particularly for shorter wavelengths, neuromodulation can only happen in the direct vicinity of the light source, and its power efficiency is relatively poor. Moreover, the integration of light sources into an implant imposes challenges on the encapsulation of the implant. Finally, the combination of gene therapy and implantation renders this neuromodulation technique less attractive for treatment purposes. A recent development is using ultrasound for modulation of neuronal activity.[90] Ultrasound experiences little attenuation in the brain and can thus modulate neural activity at greater depths. Unfortunately, given the neuromodulation mechanism is indirect (neither electrical nor chemical), its power efficiency is lower than that of electrical neuromodulation. Moreover, integration of ultrasound transducers into an implant is far from trivial.

   The network nature of the brain requires that, if modulation is applied at multiple sites simultaneously, this modulation happens with a well-controlled degree of synchronicity to have the best possible (network) response and (patient) outcome. If

the neuromodulation sites are covered by more than a single implant, this requires careful orchestration of the timing of these implants and their waveforms.

4. High-resolution neural recording: Depending on the type of neurotransmitter released and its connectivity in the network, neurons, once they fire, can have an excitatory or inhibitory effect, or no effect. To establish the desired effect on the network and thus its emergent property, the dot implants also will be equipped with high-density sensing/recording capabilities. The combination of neuromodulation and neurorecording is required for closed-loop operation,[91] through positive or negative feedback, and intelligent control. It also might help reduce the power consumption and possible side effects of the implants, given the neuromodulation can be optimized for the intended clinical application.
5. Wireless power transfer or energy harvesting: By definition, all active implants are electronic devices and thus require electrical power to execute their functionality. This energy can come from either an internal energy source, such as a battery, or an external energy source, the energy of which is coupled into the implant.

   Because of their limited energy density, batteries tend to be bulky in neuromodulation devices, which precludes their use at multiple locations in the brain (network). Moreover, once near their end of life, they must be replaced surgically, which might require a delicate surgical procedure if the implantation sites are deeper into the body or surrounded by delicate tissue. An attractive alternative is to use wireless power transfer, which can be done in the electrical, magnetic, electromagnetic, optical, or ultrasound domain.[92] Electric or magnetic wireless-power transfer (WPT), also known as capacitive or inductive WPT, uses relatively large-sized elements (compared with other techniques), such as conductive plates and coils, and hence is particularly suited for relatively large implants that are implanted superficially under the skin and thus can be in close contact with the energy source. In the case of electromagnetic WPT, much of the power radiated by the transmitter is scattered, and thus, only a fraction reaches the implant, especially when the implant is small and located deep in the tissue. Optical WPT is more suited for smaller implants but, as mentioned previously, suffers from the limited optical transparency of tissue, which decays exponentially with the distance between the transmitter and the receiver. It is therefore suited for shallow implants only that can be covered by a wearable transmitter. An exciting alternative is the use of ultrasound. As for neuromodulation, the signal experiences little attenuation along the way. Moreover, it is particularly suited for tiny implants, such as dot implants.

   A more recent approach has been to use the body's energy as a source to harvest the required energy to drive the implant, whether cardiac or brain.[93–95] Once the amount of energy that can be harvested is sufficient to power the implant fully and continuously, it is ultimately the best solution for an unlimited power supply of the system.
6. Wireless data transfer: Wireless data or information transfer, also known as wireless communication, also is crucial for driving the NeuroDots system. It requires either the generation of energy that is modulated by the information or the modulation of available energy according to the information. This latter principle also is known as backscattering or load modulation and is particularly suited for highly asymmetric communication, in which the implant is severely limited in resources (power and size) and the external device is not. It is less suitable for communication among implants in a network. The amount of data that can be communicated to and from the implant(s) per unit of time, the data rate, is linearly proportional to the available bandwidth of the communication channel and the received signal power and inversely proportional to the amount of noise and interference received. Especially for tiny implants deep into the body, this poses huge engineering challenges.[96]

   Of the five energy domains mentioned previously (electrical, magnetic, electromagnetic, optical, and ultrasonic), owing to the fundamental relation between bandwidth and carrier frequency and power efficiency, electrical, magnetic, and ultrasonic wireless communication offers lower data rates than does electromagnetic and optical power transfer. Higher data rates are particularly important in implants that have less autonomy and high demands on the number of recording and stimulation channels and on the accuracy and complexity of the waveforms acquired and generated for neuromodulation.
7. Homogeneous design: We advocate for constructing dot implants that are homogeneous in structure and in functionality. Such homogeneity will not only permit a drastic reduction of development costs and implantation effort but also a robust, mix-and-match philosophy of deployment, in which a single (or even a few) implants are not crucial to the correct functionality of the NeuroDots system because it will rely on a majority-based operation: Provided enough implants are active and in place, the system should have the desired effect. Such a strategy also has direct benefits for the system's overall robustness and dependability, to be discussed later. Then, the generic use of NeuroDots will be achieved through a combination of 1) application-specific placement (ie, the topology) of multiple, identical devices; 2) their network-level synergy; and 3) their application-specific programming.
8. Hierarchical/multiscale computing: Although homogeneous at the dot-implant level, we propose a hierarchical (and, if the application benefits, multiscale) computing architecture, ie, multiple open or closed loops, with varying degrees of processing power, latency, etc, within NeuroDots (Fig. 8).

   The original reason for imbuing implants with wireless access to the outside world was to be able to offload data logs and secondarily to be able to update the operational parameters or even firmware of those devices in the field, that is, after implantation. However, wireless capabilities have become less esoteric—eg, by adopting industry-standard protocols such as Bluetooth—and more prominent over time, allowing larger data volumes to be transferred over a longer distance.[97]

   In so doing, wireless communication has—undoubtedly—improved the quality of service of modern implants. However, in this study, we posit that it has done far more; it has instigated a paradigm shift for future implants: Although still located inside the body, implants can now expand their functionality outside the human body. They will still interact with living tissue, yet they also will be able to tap into computational and other resources available outside and often far from the patients themselves.[97] As an example, a case of a future seizure-prevention network neuromodulator located inside the human skull may be imagined. Although seizures were previously related to a single trigger area, it has become evident that they are an emergent property of a "seizure

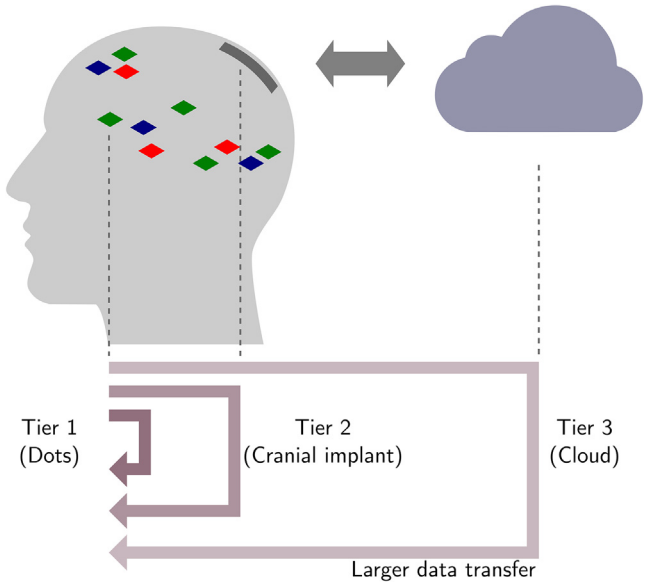


Figure 8. Hierarchical structure of a potential NeuroDots system. [Color figure can be viewed at www.neuromodulationjournal.org]

network," characterized by increased functional connectivity among different seizure nodes.[98,99] The neuromodulator records neural activity from multiple sites subdurally yet, in order to deal with the problem of timely prevention it may enlist the closed-loop synergy of all dot implants to localize and suppress a seizure onset within the "seizure network." If the local synergy is not enough to properly identify and stop the seizure owing to any number of reasons, it also may enlist the clinical statistics residing in some remote resource for proper seizure detection, subject to patient age, sex, or even geographic location. This may require the added processing power and centralized overview of a master (cranial) implant coordinating and aggregating the data from all other dot nodes. That implant should be closer to the skull (eg, similar to the modern RNS System, NeuroPace Inc., Mountain View, CA[100,101]) and should be equipped with higher computing and wireless capabilities.

Federated or collaborative learning and other distributed strategies[102,103] could be facilitated by such an implant. If this slower but more powerful loop is still not sufficient, or if more systemic phenomena are occurring outside the strict purview of the implant network—eg, patient stimulation parameters have drifted, a local patient group exhibits different seizure patterns due to a change in living conditions such as conflict, pollution, traffic, regional medication policies—implant-system functionality has to expand again, now outside the patient and into wirelessly collaborating resources, eg, Big Data available in a medical data lake in the Cloud. Trying to understand the patient's "local" readings may then become much easier by comparing them with (anonymized) population-wide statistics. Through even more powerful computing capabilities in the Cloud, such comparisons can help indicate a drift in operational parameters, in patient-specific or time-sensitive stimulation strategies, and so on. Obviously, closing the loop in this extended fashion cannot take place in real time and introduces system-availability concerns. However, such extended operations should not be compulsory or time-critical and should take place very rarely by implant duty-cycle standards, eg, once per week. In such a paradigm, multiple, nested closed loops exist in parallel and collaborate among them, with the system hierarchy requiring topical, weaker, faster, high-criticality loops but also geographically relaxed, compute-intensive, slower, lower-criticality ones.

This has direct technical implications not only for the computing paradigm of future implantable systems (eg, federated learning inside the skull, Big-Data analytics complementing neuromodulation in pseudoreal time) but also for the wireless energy- and data-transfer technologies used. An asymmetry appears in the resources versus the transmission capabilities of the two sides of the spectrum: Tiny implants will need to transfer (proportionally speaking) large volumes of physiological data upstream, whereas a powerful Cloud server will process the data and decide, which usually translates to simple or little data traveling downstream.

9. Adaptive and self-learning devices: The above requirement makes it obvious that the NeuroDots system must detect patterns in the acquired signals. The problem of pattern recognition in neural signals is well studied in the literature and has received renewed interest owing to the emergence of deep neural networks (eg, [104–108]).

However, in the context of networked devices that also are potentially connected to the Cloud, the devices can cooperate, and certain computations can be delegated to the Cloud. Such a distributed setting leads to interesting questions from the viewpoint of artificial intelligence (AI). For instance, which parts of the data processing and AI modeling shall be done by individual devices? What AI computations can be done jointly by multiple devices in tandem, and what AI processing can be carried out by the cloud?[109] If data from devices implanted in many patients are available, AI models can be trained in real time on data from multiple patients. This may lead to more accurate machine-learning models if data for a particular patient are limited. A model can be trained first on data from other patients and then be fine-tuned on data of the target patient by means of transfer learning. AI has improved tremendously in its decoding accuracy of neural signals. For example, acute and chronic pain can be detected with 94%[110] and 93% accuracy,[60] respectively, whether one uses functional magnetic resonance imaging (fMRI)[110] or electroencephalogram (EEG).[60] Similarly, EEG can detect tinnitus with 88%,[60] Parkinson's disease with 94%,[60] and depression with 75% accuracy.[60] Even more complex AI approaches, such as speech decoding in a patient with stroke, reach impressive results.[111]

To reduce the communication load and protect the privacy of the patients, one could train AI models locally on each device individually and only share the parameters of the model across the different devices, instead of sharing neural data. The framework of federated learning[109] provides algorithmic approaches for distributed learning of AI models based on data stored at multiple sites. Although federated learning is usually applied in the context of medical data sets that are safeguarded at multiple hospitals, it also can be explored in the context of multiple devices that gather neural data, whereby AI models are trained on data from those devices without sharing neural data among the devices.

10. Efficient data reduction/handling: The implantable nodes will generate a data deluge that must be efficiently and effectively dealt with. Ideally, one would want to reduce the data volume as much as possible while preserving information for self-learning and closed-loop control in later steps in the process. This is precisely the objective of data compression, a well-studied topic in the fields of signal and information processing and information theory.

    Data compression can be classified into two major categories:[112–114] lossy and lossless compression. The former discards some components of the neural signals and therefore compresses the signals substantially, whereas the latter allows perfect reconstruction of the neural data and consequently only modestly compresses the original data. For clinical applications, exact reconstruction of neural signals is more important than data reduction. In other applications, lossy compression may be more suitable. A compelling compromise between lossless and lossy compression is "near-lossless" compression:[112] Attractive compression rates (eg, 3–10) can be achieved whereas the distortion remains acceptable. In near-lossless compression, no sample in the reconstructed signal is changed in magnitude more than a fixed, positive tolerance level compared with the original sample. Neural signals are typically analyzed by visual inspection by human experts and/or by automated analysis using signal processing and machine learning algorithms. Therefore, compression of neural data would only be suitable if compression does not introduce any errors in such analysis. In this context, near-lossless compression is often adequate, given the user can control the maximum amount of distortion.

    For the design of compression schemes for multisensor neural data, there are the following desiderata:

    a. As alluded to above, the distortion in each signal sample should be below a tolerance set by the clinician (near-lossless compression).
    b. The compression scheme should exploit the inter- and intrachannel correlation, ie, the correlations over time and across the different sensors (channels).
    c. The compression scheme should support progressive transmission, in which the first transmitted bits allow a coarse reconstruction of the neural data, and gradually, the quality of the reconstruction improves as more bits become available. In other words, the bitstream can be truncated at any point below the encoded rate to give the best quality reconstruction at that particular rate.

    In the following paragraphs, we briefly address each of these three properties. Near-lossless compression algorithms typically comprise two stages:[112] First, the multisensor data are subjected to lossy compression; second, the residual of the lossy reconstructed data is quantized and compressed in a lossless fashion (often by arithmetic coding). The latter step makes it possible to bound the distortion on the residual for each individual sample and hence also the reconstructed neural data.

    Inter- and intrachannel correlations can be exploited by arranging neural data in matrices or tensors.[112–114] Once the data are arranged in this multidimensional manner, they can be analyzed by matrix and tensor decomposition methods[112–114] or through deep learning in neural networks.[115,116] An alternative framework is compressed sensing,[117,118] which relies on sparsity in the (potentially multidimensional or multiscale) representations of signals.

    Progressive transmission can be achieved by representing the neural data on multiple scales, such as discrete or continuous wavelets[112] or Gabor decompositions.[119] By decoding the lowest scale in the representation first, followed by the higher scales, the signal reconstruction gradually improves as more data are received.

    Besides the algorithmic aspects, another challenge is to design compact and energy-efficient hardware to support compression of neural signals[120,121] in which compression could be performed at the sensors directly. Moreover, instead of processing and compressing all neural data, only relevant events in the signals could be compressed and transmitted (eg, epileptic seizures), reducing the overall computational and communications load of the neural platform.[121]

11. Secure computation and communication: The data generated by the dot implants introduced in the above section are highly sensitive and private. The most natural form of securing these data is using wired communication. However, in the case of wireless dot implants, additional measures must be used to properly secure the wireless interface from eavesdropping, malicious implant access, data tampering, and so on. Unfortunately, these tiny implants have very limited computational resources to execute the computationally expensive cryptographic primitives needed to secure wireless communication. This calls for using unconventional security solutions for this purpose.

    For example, we discussed that ultrasound is being touted as an in-body communication channel between these implants. This channel is inherently secure when the popular MHz-range ultrasound transducers are used.[122] This can relieve the need to use any cryptographic computations on these implants.

    However, ultrasound offers limited bandwidth and thus data rates, and is severely attenuated by the skull. As a result, additional (cranial) implants need to be used that interface the tiny dot implants with the outside world. More specifically, for the previously mentioned security solution, a communication medium other than ultrasound is required when talking to an external wearable device. This also implies that these cranial implants must be larger than the dot implants to house the cryptographic primitives needed to secure the external wireless channel. This will be discussed in more detail. Another reason for their larger size is that they require higher transmission powers and thus more energy storage, to handle greater data rates and distances.

12. Dependable operation: By definition, every life-critical system such as a medical implant needs to come with sufficiently high levels of dependability, and so does NeuroDots. However, in this study, we will mostly focus on two levels of dependability for NeuroDots:

    a. At the device level: Dot implants must be resilient and robust, ensuring chronic and correct functionality. Various techniques can be used, including hardware and software fault tolerance.
    b. At the network level: Combining multiple identical dot nodes, device failure rates can be better controlled, and what is more, graceful degradation through self-organizing implants can be achieved. If one or a few devices fail, the

rest can continue effecting network neuromodulation, perhaps at some diminished effectiveness but certainly not failing catastrophically. This property shall be achieved by providing some redundant nodes to the NeuroDots network. Interestingly enough, the dot redundancy to some extent shadows the redundancy of the biological brain.

The above extensive list of technical requirements offers a more rigorous outline of the vision for NeuroDots implants of the future. However, such specifications would be futile should they fail to address the original list of clinical requirements delineated in section 4. To that end, we next plotted a cross-tabulation among the NeuroDots clinical and technical requirements (Table 1). The main idea is that each line is covered by ≥one column, to guarantee feasibility and clinical relevance; it is this aspect that has been mostly overlooked in current works so far.

TAXONOMY OF NETWORKED-NEUROMODULATION SYSTEMS

The clinical and technical requirements presented in the previous sections elicit the need for a generic, implantable system architecture that offers a comprehensive coverage of the said requirements. To find this ideal solution, we first list possible system architectures (or topologies) and explain the reason we believe that only a subset of those are realistic. These topologies are summarized in Figure 9 and explained in the next section.

Topology 1 (Dot Implants Only)

The first topology refers to the ideal case, in which millimeter-sized dot implants directly communicate with the outside world (ie, the cloud through a portable device, eg, a smartphone; Fig. 9) However, power-transfer and communication bottlenecks render this configuration unrealistic for the foreseeable future. Regarding powering such nodes, it is still a challenge to design millimeter-sized batteries for such implants. In contrast, continuously transferring power wirelessly from the portable device is unrealistic; a hazardously large amount of power must be applied for the required amount to effectively reach the dot implants. In addition, for many recording channels per dot implant, it would become infeasible for the dot implants to directly transmit the bulky recorded data to the portable device without relentless data compression. Moreover, this compression or dimensionality reduction is infeasible to implement on these tiny nodes because they are severely limited in resources for the needed computation. In addition, for high usability, it makes sense to use the technologies that are already available on the portable device, such as Bluetooth, near-field communication (NFC), etc. However, these technologies and respective security standards are still too bulky to be executed on these millimeter-sized nodes, eg, owing to computational and security requirements, transmit powers, area requirements, etc.

Topology 2 (Dot Implants + Cranial Implant)

In this topology, a cranial implant is added between the dot implants and the external world. This cranial implant has a battery and can wirelessly transfer power to the dot implants while acting as a communication relay between them and the outside world.

Table 1. Correlation Between the NeuroDots Clinical and Technical Requirements.

Technical requirements	Clinical requirements									
	Multisite	Multifunction	Highly autonomous	In vivo reprogrammable	Data logging	Generic in use	Minimally invasive	Chronic operation	Biocompatible	Ecologic
Large coverage	•	•			•		•	•	•	•
High elasticity and biostability	•						•	•	•	
Efficacious neuromodulation	•	•	•		•	•				
High res. recording	•	•		•	•					
WPT	•		•				•	•	•	
Wireless data transfer	•	•	•	•	•		•	•		
Homogeneous design	•	•				•				
Hierarchical computing	•	•	•		•	•	•			
Adaptive and self-learning devices	•	•	•		•	•				
Efficient data reduction/handling	•			•	•			•		
Security	•			•	•					•
Dependability	•		•	•				•	•	•

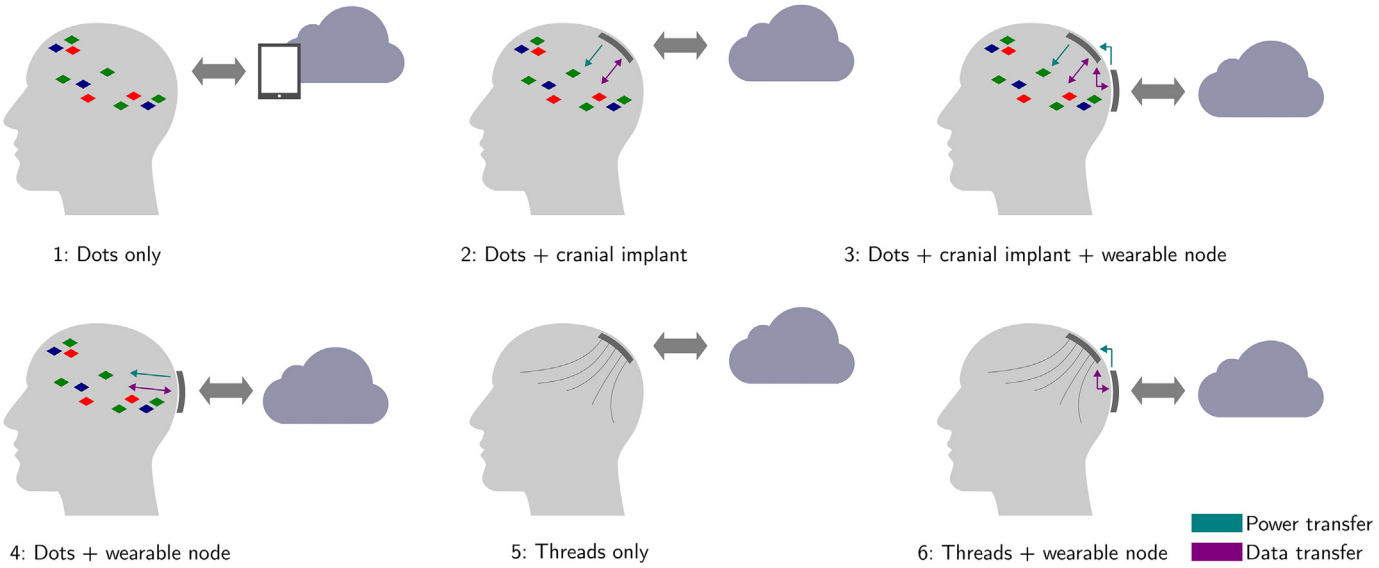


Figure 9. A taxonomy of networked-neuromodulation systems. [Color figure can be viewed at www.neuromodulationjournal.org]

Because the cranial implant is significantly larger in size than the dot implants, it can run more complex algorithms to provide a local closed loop. This also reduces the amount of data that needs to be transmitted externally. Finally, compared with topology 1, the security requirements on the dot implants can be relaxed, given usually a very localized and short-range communication channel is used to interface the dot and cranial implants. In case a non-rechargeable battery is used in the cranial implant, the operational lifetime of the system is limited unless another surgery is performed to replace the battery.

Topology 3 (Dot Implants + Cranial Implant + Wearable Node)

In this topology, a wearable component is added that holds the battery, whereas the cranial implant only has an energy reservoir and acts as a relay node between the dot implants and the wearable node. The main advantage of this configuration is that it will allow reduced invasiveness for improved physical access and thus for improved maintainability and easier (re)charging or battery replacement. However, the patient is now required to wear the wearable device, which affects usability. The remaining considerations are the same as for topology 2. Some examples of the implantable portion of this topology include the neural dust and neurograin approach.[123] However, it should be noted that their focus is only on implant miniaturization, WPT, and data communication among the different tiers.

Topology 4 (Dot Implants + Wearable Node)

This topology comprises dot implants and the wearable device, and it avoids the implantation of a cranial node. However, such a scenario has its own engineering challenges given it is difficult to transfer power and communicate directly with the deeply implanted dot nodes. Specifically, ultrasound-based power transfer might not be feasible if the skull (which is opaque to ultrasound) is present between the dot implants and the wearable node. The (in)feasibility of ultrasound also affects the available communication options; ie, it cannot be used as a communication channel. Consequently, security also becomes a concern because the communication channel used (ie, other than ultrasound) will be vulnerable to eavesdropping. This is because alternative communication mediums, such as radio frequency, are not inherently secure like ultrasound. This implies that the dot implants must encrypt the data to secure the communication channel with the wearable device, which complicates the design of these small devices.

Topology 5 (Threads)

There are no dot implants in this topology. However, there are deeply implanted electrodes that are connected with a cranial implant through thin threads. The advantage of this topology is that there is no processing power required near the electrodes, and thus, all the computations can be localized at the cranial implant. Moreover, the wired connection between the electrodes and the cranial implant eliminates the wireless transceivers and the associated challenges. Other characteristics of this topology include data compression not being required at the electrode level given it is not being transmitted wirelessly. The wired connection also implies that the data transmitted through the threads are inherently secure. The downside of this topology is that the implantation of these wires originating from one location to different locations spread over the brain is unresolved. We term this the spaghetti problem. Moreover, as with topology 2, surgery is required to replace the cranial implant in case of a non-rechargeable battery. Example systems include the RNS System[101] and the more advanced TRANSFORM DBS, which is not yet commercially available but is supported by the DARPA SUBNETS program.[124] The TRANSFORM DBS system has a central hub, multiple satellite processors for digitizing and routing neural activity, a transceiver, and a base station. The central hub incorporates centralized processing, power, communications, and stimulus pulse generator. It can connect to ≤five satellite systems,

each with 64 channels, providing ≤320 channels for stimulation or recording.[124]

Topology 6 (Threads + Wearable Node)

Compared with topology 5, this topology has a wearable node that communicates with the cranial implant (similarly to topology 3). As a result, the cranial-implant battery can be moved to the wearable node, which resolves the battery replacement issue of the previous topology. However, now, the patient must continuously wear this wearable device, which affects usability. Example systems include Neuralink (Neuralink Corp., Fremont, CA)[125,126] and Neuro-stack.[127,128]

The Neuro-stack comprises a wearable bidirectional closed-loop neuromodulation system and can be used to record single-neuron and local field potential activity during stationary and ambulatory behavior in humans by recording from ≤256 contacts for a total of 128 monopolar or bipolar recordings with a sampling rate of ≤6250 Hz. It also has a highly flexible and customizable stimulation capability and can perform closed loop stimulation by detecting θ power.[127,128]

MAKING THE CASE FOR THE RIGHT TOPOLOGY FOR NEXT-GENERATION NEUROMODULATION

A summary of different topologies previously discussed and a qualitative comparison are presented in Table 2. This comparison was performed on the basis of the previously mentioned clinical and technical requirements. The top row of the table is a condensed form of the clinical and technical requirements. For example, battery replacement is derived from chronic operation and dependability requirements.

At first look, topologies 5 and 6 seem to be the most preferable, given they have the minimum number of shortcomings. However, one of those shortcomings is the spaghetti problem, which we consider extremely critical: A fine balance between stiffness during insertion (for preventing buckling of the electrode arrays and reducing tissue damage) and flexibility after insertion (for reducing tissue damage due to micromotions of the brain) needs to be found, which is not trivial.[129] Furthermore, in the published literature[125,126] or on the Neuralink website, no information can be found that these devices, which have a very high spatial resolution, adapt their stimulation design to the recorded activity from the entire network, ie, correlated or anticorrelated, rather than adjust their output to the recorded information from the individual electrodes of the singular implant. If this potential to coordinate with other electrodes of the network is not built into the devices, it is nontrivial to add this at a later stage because it will significantly affect the design and functionality of the implant.

After inspecting the rest of the topologies, which do not have the spaghetti problem, we find that topology 3 causes the minimum cost since it scores the highest in terms of maintainability, and (re)charging or battery replacement. Topology 2 performs similarly to topology 3 but scores higher on user acceptability. Therefore, topologies 2 and 3 can be regarded as the most feasible for NeuroDots. Topology 2 is superior if battery replacements are not an issue, and considering 1) battery capacity improves steadily and 2) that patients with neuromodulation devices will want them to work and to forget about them,[130] analogous to patients with current DBS who prefer a non-rechargeable, implantable pulse generator (IPG),[131,132] as one

Table 2. A Qualitative Comparison of the Different Topologies of Networked-Neuromodulation Systems.

Topology	IMD compute complexity	IMD-communication complexity	IMD powering complexity	Security	Usability and user acceptability	Battery replacement	Minimally invasive	Node stability	Spaghetti-problem avoidance	Reprogrammable	High synchronicity
1: D	–	–	–	–	++	++	++	–	++	-	-
2: D+C	–	+	+	+	++	–	–	–	++	-	-
3: D+C+W (e.g., Neural Dust, NeuroGrain)*	–	+	+	+	–	++	–	–	++	-	-
4: D+W	–	-	-	–	–	++	++	–	++	-	-
5: T (e.g., NeuroPace)	++	++	++	++	++	–	–	++	—	++	++
6: T+W (eg, NeuraLink)	++	++	++	++	–	++	–	++	—	++	++

The box ranges from best to worst performance in the following sequence: ++, +, -, –, and —.
C, cranial implant; D, dot implant; IMD, implantable medical device; T, threads; W, wearable node.
*It should be noted that such works are only focused on implant miniaturization, WPT, and data communication among the different nodes.

reviewer kindly suggested, it becomes evident that we ultimately select topology 2 as a template for the development of a prototype.

It is noteworthy that landmark works such as Neural Dust and Neurograin fall under the similar topology (topology 3), so one might wonder what the reason for proposing NeuroDots implants is. As discussed above, these technologies—although interesting in their miniaturization efforts—fall short of tackling the practical aspects of using such miniature devices. Moreover, previous works in this domain are putting the cart before the horse in terms of targeting medical discovery; there is a lack of governing hypotheses on ways such devices should work collaboratively, a similar problem for the Neuralink device, to tackle challenging neurologic problems. However, and as we hope to have sufficiently shown in this manuscript, the small-network model of the brain has direct implications for the clinical and technical requirements of dot implants.

CONCLUSIONS

Novel insights in the way the brain functions as a complex adaptive (neuroplastic) system propose that neurologic and psychiatric disorders are emergent properties of networks and not the result of one phrenologically abnormally functioning area in the brain.[1,2] Neurologic and psychiatric disorders are thus characterized by abnormal functional and effective connectivity within and among ≥three canonical networks in the brain.[4,5,43] These abnormal functional connections can be correlated or anticorrelated.[42]

On the basis of network science,[62] it can be shown that targeted attacks on the connector hubs have the highest likelihood of disrupting abnormal connections and rebuilding physiological interactions.[133]

This requires a whole new breed of interacting networked neuromodulators that must fulfill a set of requirements to generically treat neurologic and psychiatric disorders by normalizing maladaptive functional connections within and among networks and reconstructing correlated and anticorrelated activity.

It is evident that the development of NeuroDots will require a staged approach, but the vision described permits ensuring that all essential ingredients of the NeuroDots are ready to be implemented in each phase of the development, rather than "climbing Mount Improbable,"[134] ie, having to redesign hardware features whenever a novel feature of the optimal NeuroDots system is ready to be released.

Authorship Statements

Dirk De Ridder prepared the neurobiological part of the manuscript draft (sections 1, 2, and 8). The engineers Muhammad Ali Siddiqi (cybersecurity and computer engineering), Justin Dauwels (computational neuroscience, AI), Wouter A. Serdijn (Bioelectronics), and Christos Strydis (computer engineering and neuroscience) prepared sections 3 to 7. All authors reviewed, rewrote, and approved the final manuscript.

Conflicts of Interest

Dirk De Ridder serves as a consultant for Abbott and has received payment or honoraria for lectures or presentations for Abbott, including support for attending meetings and/or travel. Dirk De Ridder has submitted patents on sensing and network stimulation as well as noise and-nested stimulation. The remaining authors reported no conflict of interest.

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COMMENT

The authors provide an interesting speculative study concerning where we all should be heading with DBS or more accurately, brain modulation. Their main point is that we need to move past the era of sticking an electrode in a nucleus, adjusting the stimulation parameters, and hoping for the best. Network dysfunction needs to be addressed. The authors discuss various methods of energy delivery, information transmission, and power supply. Readers should see this article as a challenge to us all to advance the science and art of brain stimulation, and to work as best we can toward bringing in the next era of neuromodulation.

Michael Schulder, MD
New Hyde Park, NY, USA