# Sensory Neuromodulation

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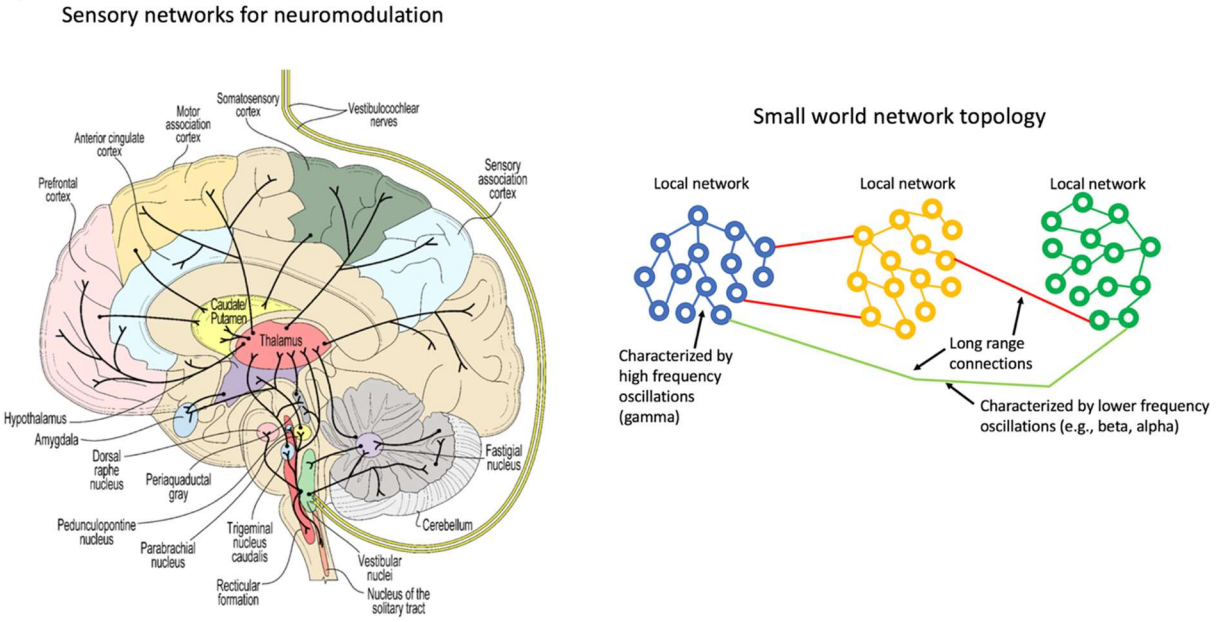
Abstract: We describe a model of neurological disease based on dysfunctional brain oscillators. This is not a new model, but it is not one that is generally appreciated by clinicians. The value of this model lies in the predictions it makes and the utility it provides in translational applications, in particular for neuromodulation devices. We provide a perspective on the difference between neuromodulation devices that enforce an externally administered stimulus with devices that provide input to sensory receptors and thus stimulate endogenous sensory networks. Current forms of clinically applied neuromodulation are of the former type, including devices such as (implanted) deep brain stimulators (DBS) and various, noninvasive methods such as transcranial magnetic stimulation (TMS) and transcranial current methods (tACS, tDCS). The challenge with these methods is that they are not sensitive to underlying neuronal dynamics and work by applying an empirically derived electrical current waveform to affect dynamical patterns. Neuromodulation of a sensory organ accesses the same pathways that natural environmental stimuli do and, importantly, the modulatory signal will be transformed as it travels through the brain, allowing the modulation input to be consistent with regional dynamics. We present specific examples of devices that rely on sensory neuromodulation and evaluate the translational potential of these approaches. We argue that sensory neuromodulation is well suited to probe and, ideally, repair dysfunctional brain oscillators, thus providing a novel therapeutic approach for neurological diseases.

*Keywords*: neuromodulation, noninvasive, sensory networks

Graphical Abstract:



**Part 1: Oscillatory Dynamics**

There is now growing evidence that brain dynamics are underpinned by collective oscillatory states. In this monograph, we explore the proposal that neurological disease can be modeled as dysfunctional brain oscillators. We further consider how artificial neurostimulation methods might alter brain oscillators and the potential for improving functional deficits resulting from disease. Most particularly, we examine neurostimulation introduced into an endogenous sensory network and examine how this approach is categorically different from current clinical methods of neuromodulation.

Neuronal oscillations:

The observation of neuronal oscillations has been documented in relatively simple animals such as aplysia (Elmariah, 2007) and jelly fish (Nath, 2017). EEG recordings have been reported in eels (Barthelemy, 1977), fish (Robb, 2003) and reptiles (De Vera, 1994). De Vera et al. (1994) suggested a homology between the waking state of reptiles and slow-wave sleep in mammals. This is an evocative suggestion, but the primary finding is that oscillations enable behavior in animals in a manner that cannot be deduced based simply on the static architecture of the connectome.

Though EEG recordings have been studied for decades since the original work by Berger in the 1920's, their significance was not immediately understood. Until recently many researchers were unsure of whether the oscillations recorded in EEG time series were meaningful or simply epi-phenomena of Hebbian firing patterns. Fries (2005) proposed that oscillatory activity in the brain is actually central to function, enabling a means by which transient pathways can form and fade, based on demand. His communication through coherence model provides an elegant answer to the question of how *dynamic* organization of the cortex occurs. More recently, McLelland & VanRullen (2016) reviewed communication-through-coherence and refinements.

Buzsaki's (2006) comprehensive book takes a consistent, oscillation-centric perspective on the primacy of oscillations to brain function. He starts with a general review of periodic, nonlinear and chaotic phenomena in nature and from that develops a framework for understanding coupled oscillators and details results from invasive neuroscience studies before turning to non-invasive methods used in human research, including EEG, MEG and functional imaging. He paints a story of continuity, both evolutionarily and architecturally, from small clusters of neurons to the whole brain. Voytek & Knight (2015) suggested that dynamic network communication relies on coordination via neuronal oscillations, the disruption of which can result in clinical disorders. Assenza et al. (2017) and Fox et al. (2014) reiterated the view that dysfunctional brain oscillators are associated with disease and they review how neuromodulation may be helpful in altering and improving brain oscillator function.

There is a significant literature that has applied oscillator models to biological systems, or rather has attempted to understand biological processes with simplified oscillator configurations. Winfree (2001) and Kuramoto (1984) looked at the phenomenon of synchronization of biological oscillators, providing mathematical models for quantifying when synchrony can occur and what that may imply for studies of actual neuronal networks. Watts & Strogatz (1998) showed that the collective dynamics of so-called "small-world" networks could be used to explain the collective pathways observed in the brain**.** The essence of small-world topology is that most connections are local and sparse long-range connections allow for global communication (figure 1). This form

seems very well matched to the observation that gamma oscillations enable localized neuronal dynamics and slower (alpha, beta, etc.) EEG frequency bands are indeed associated with longer-range dynamics. The small-world topology is an optimal configuration for the efficient use of space (synaptic density) while still enabling global communication.

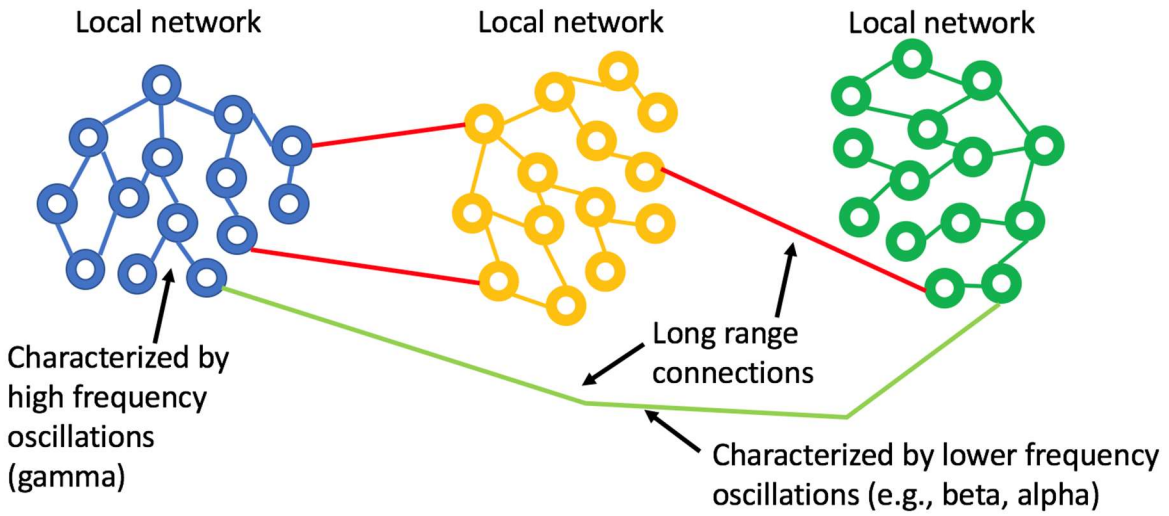



*Figure 1: Small world network topology. The highest density of synaptic connections is local and longer-range connections are sparse. This topology is consistent with high frequency, short-range oscillations (gamma) being local and longer range, slower oscillations being regional or global.*

CFC - Cross frequency correlation:

Entrainment of an oscillator at its natural frequency means that there is energy transfer between the driving or exciting oscillation and the target oscillator (figure 2). An everyday example is the way a child "pumps" a swing until the natural frequency of the swing is reached and thereafter little additional effort is needed to maintain entrainment. A small but consistent excitation source is able to entrain an oscillator near its natural frequency and this efficiency is realized in brain oscillators as well (e.g., Buzsaki, 2006). Via a phenomenon called cross-frequency coupling (CFC), it is also possible to entrain oscillators that don't have the same natural frequencies. Instead, CFC describes coordination of different oscillators whereby both oscillators have modified dynamics. Figure 3 shows an example of CFC between a fast and slow oscillation. The slower oscillation modulates the amplitude of the faster, and the faster makes ripples in the slower. This behavior has been recorded in brain oscillators, for example in CFC between gamma and beta frequencies (de Hemptinne et al., 2015). There are several forms of CFC that may have analogs in brain dynamics (Aru et al., 2015). CFC underpins the long-range connections described by the small world network model.

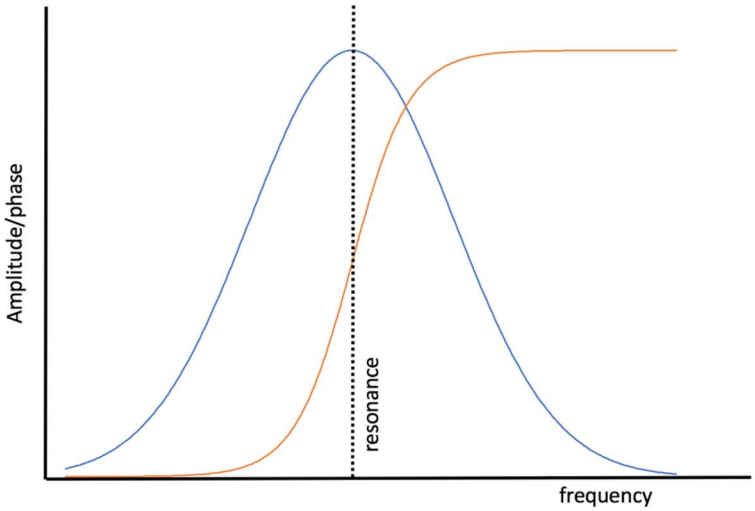



*Figure 2: The behavior of a simple, undamped oscillator as a function of excitation frequency. The amplitude of the response of the oscillator (blue) to the driving force peaks when the driver reaches the natural resonance of the oscillator. The phase of the oscillator with respect to the driver (orange) is in phase when the driving frequency is lower than the resonant frequency and anti-phase when the driving frequency exceeds resonance.*

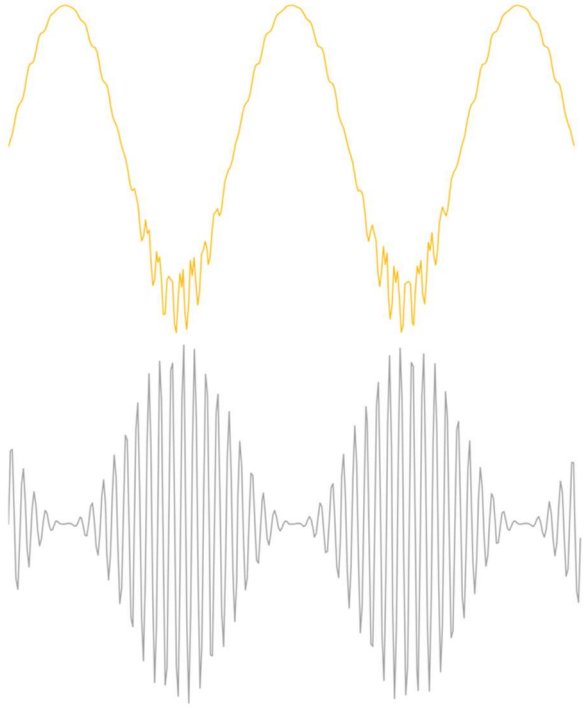


*Figure 3: Example of Phase Amplitude coupling, one form of CFC. The top figure illustrates the effect of coupling on beta oscillations where the bottom figure represents gamma oscillations. Beta modulates the amplitude of gamma and gamma perturbs the envelope of beta. CFC is essential for normal brain function, but over or under coupling can be pathological.*

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The formation of dynamic small-world ensembles is partially facilitated by developmentally established neuronal pathways, but the transient selection of certain subsets of all possible pathways must rely on an encoding scheme. How might encoding and recall be enabled in an oscillator-based model? Hoppensteadt & Izhikevich (1998) provide a simple yet general schema that models thalamocortical interactions via weakly coupled oscillators and they develop an intuitive framework in analogy to FM radio principles. A primary insight from their model is that a cortical oscillator may participate in different ensembles by changing its frequency without changing the strengths of synaptic connections. The authors also clarify the point that the terms "inter-spike intervals," "frequency modulation," and "phase modulation" all describe the same thing, in the neuroscience, electrical engineering, and mathematical physics literature respectively, even though that unity of description is not generally appreciated (figure 4). The crucial observation is that frequency and phase encoding are both biologically plausible as means for creating the sort of transient neuronal ensembles that are consistent with oscillator-based theories of brain function. The particulars of how frequency and phase encoding are instantiated in real brain networks are not yet fully understood, but established analytical methods from past studies of oscillatory networks provide a fertile basis for model generation.

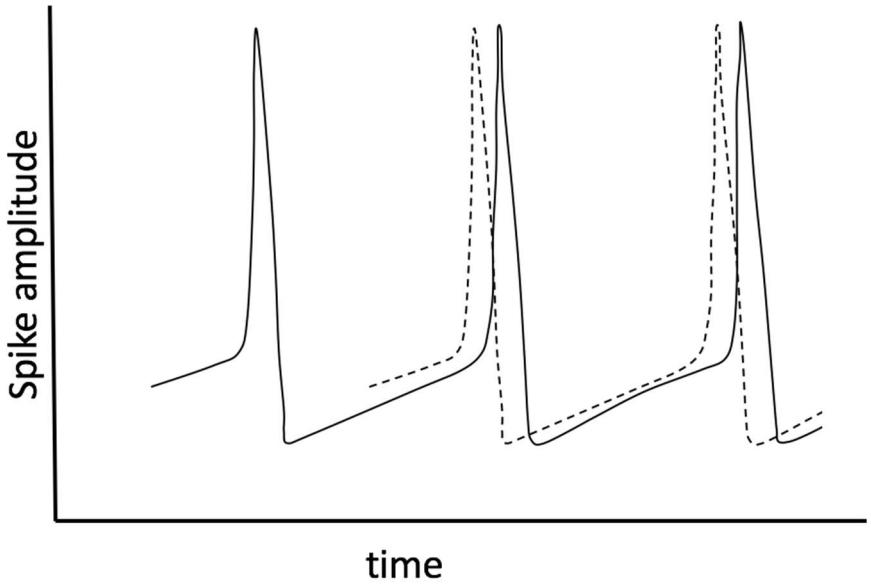


*Figure 4: Spiking of a relaxation oscillator (the basis for the Hodgkin-Huxley model), where an applied perturbation has shifted the phase of the spike train. This shift can be viewed as a change in spike timing, phase modulation, or frequency modulation: they are all equivalent mathematically. Adapted from Hoppensteadt & Izhikevich (1998).*

To summarize, can we view neurological disease as *resulting from* dysfunctional brain oscillators? The test of any model is whether it has predictive power and, clinically, whether it informs delivery of therapy. And so we can now ask whether it might be possible to interface with and alter oscillatory brain networks in order to achieve a clinical benefit. Understandably, this is a very different therapeutic perspective from one based on looking for discrete biochemical pathways and trying to alter them, selectively, using an exogeneous pharmaceutical agent. How would one know which oscillators to affect and how would such an interaction provide a benefit, versus being neutral or negative in effect? We will survey current neuromodulation approaches and then introduce the concept of sensory neuromodulation as a distinct format that may be particularly

well matched to the challenge of interfacing with brain oscillators. Additionally, we will look at some evidence that suggests that taking an oscillator-centric view of neurological disease might also provide insights into innate protective pathways in the brain that orchestrate underlying biochemical processes. That is, it may be that the brain is able to marshal a biochemical response to repair and maintain neurons in response to the aberrant firing patterns of damaged brain oscillators.

**Part 2: Methods of Neuromodulation**

There are several recent and excellent reviews of clinical neuromodulation (see the Workshop summary under Bain et al., 2015, and references therein). Deep brain stimulation (DBS) describes a category of interventions seeking to alter regional neuronal activity via a surgically implanted electrode powered by an implanted pulse generator. Non-invasive brain stimulation (NIBS) describes a class of devices that use externally placed electrodes to direct electrical current into brain (usually cortical) tissue, that current being direct or alternating. Transcranial magnetic stimulation (TMS) makes use of a rapidly changing magnetic field to induce current flow in the cortex and as such is a method that does not require direct contact to the head. These methods have been used extensively in a research context and there has been translation to clinical medicine as well. DBS, especially for movement disorders associated with Parkinson's disease, is a well-established approach, but it is typically reserved for late-stage disease because of the invasive nature of the placement procedure and the concommitant high cost (Umemura et al., 2016). TMS has been cleared by the FDA for major depressive disorder (Connolly et al., 2012) and for migraine headache (Conforto et al., 2014). Two other alternating current methods have been cleared for the treatment of migraine headache, one using an applicator on the neck for stimulation of the vagus nerve (Silberstein, 2016) and another applying current to the forehead (over a branch of the trigeminal nerve; Schoenen et al., 2013). Despite these clinical successes, there is a general concern about the design of NIBS studies and the need for a comprehensive approach that includes attention to the mechanism of action for a given intervention (Frohlich & Schmidt, 2013).

How do these neuromodulation methods interact with and/or alter brain oscillations Current forms of clinical neuromodulation work by applying an empirically derived stimulation waveform or pulse sequence. A parallel goal is to avoid the induction of paresthesia or other unwanted side effects. That is, there is no *a priori* theoretical knowledge of why a certain stimulation pattern will be effective. An empirical approach to the choice of the stimulation parameters has been used for DBS therapy since its inception. Vosskuhl et al. (2018) used tACS with the goal of entrainment and the induction of neuroplastic modification, focusing on the effects of different applied waveforms. Thut (2014) considered directly interacting with brain oscillations, using NIBS, to alter function, stating that neuronal oscillations drive sensory experience versus the sensory experience driving the oscillations. Obviously sensory input results in changes in brain oscillations, but the author's point is that the computational aspects of perceiving sensory information is predictive and is mediated by brain regions separate from the primary sensory cortices. Thut et al. (2017) recommended the use of EEG and MEG to guide the application of transcranial electrical stimulation so as to take account of the phase and frequency of a targeted brain oscillation. Despite the additional challenge of needed to monitor the dynamics of brain oscillations suggested by the authors, the applied stimulus affects nerves in proximity to the electrodes, but does not necessarily reflect the endogenous activity patterns of those nerves. Ali

et al. (2013) summarized the challenge of matching an exogenously generated stimulus to the target brain oscillator: "An important implication of this finding is that the frequency of applied stimulation should be matched to the frequency of the endogenous oscillatory state.…[and] the choice of stimulation frequency could represent a serious challenge as there is no clear preferred resonance or peak frequency." We propose that neuromodulation of a sensory network addresses this matching challenge. If the brain target is accessed by endogenous neural (sensory) pathways and the modulation signal is applied to the sensory organ, the modulation is transformed in a way that it is matched to the native dynamics of the target region.

That a sensory system processes and transforms incoming stimuli is perhaps most intuitively understood by considering vision. The light pattern on the retina changes rapidly as the result of saccadic eye movements and these signals follow the optic nerve to the first visual cortical region (V1). The visual scene is broken into constituent elements, as was described in the seminal work by Hubel & Wiesel (1959) and further processing proceeds in a hierarchical fashion. Near the top of the visual hierarchy, the brain is able to maintain a persistent representation of a viewed object even though the input activity patterns from the retina itself do not match the activity patterns in that part of the cortex representing the viewed object (Wurtz et al., 2011). The retinal signals were transformed and combined with input from other brain regions with the net effect that a new dynamic oscillatory state consistent with the represented object emerged. It is this sort of transformation of raw sensory inputs into meaningful patterns at the targeted brain region that marks the difference between sensory neuromodulation and other current formats. There is no way to emulate these detailed, regional signal transformations with exogenously applied stimulation methods (NIBS) with just one or a limited number of frequencies.

Visual, auditory, somatosensory and vestibular neurostimulation methods are described in the literature and we now evaluate examples of clinical studies with translational intent to better illustrate *sensory neuromodulation*.

A well-described method for modulating visual perception makes use of an optokinetic drum, a rotating cylinder with light and dark stripes that is viewed by a subject. Most commonly an optokinetic experiment aims to induce perceptions of self-motion and nystagmus. Kikuchi et al. (2009) performed optokinetic stimulation while acquiring BOLD MRI data and demonstrated activation of cortical areas related to visual movement processing and deactivation of the parieto-insular cortex, which is primary in vestibular processing. Chokron et al. (2007) described studies using optokinetic methods for mitigating unilateral spatial neglect. The general aim was to correct spatial bias by realigning perception of spatial coordinates. The authors review a number of such studies and conclude that the effects were transient when single sessions were used. Kerkhoff et al. (2006) performed longitudinal optokinetic stimulations and reported persistent improvement over a 2-week follow up period, which may imply a neuroplastic change as the basis for durability. Iaccarino et al. (2016) presented evidence in support of the reduction of plaque formation in a murine model of Alzheimer's disease via optogenetically driven modulation of interneurons in the gamma frequency range. This is an interesting case wherein changes in oscillatory stimulation trigger a protective biochemical response. Using neuromodulation to activate neuroprotection is a topic to which we will return later.

Marks et al. (2018) evaluated the application of simultaneous auditory and somatosensory

stimulation as a treatment for tinnitus. Starting with a guinea pig model, the authors found that fusiform cells exhibited increased spontaneous activity and cross-unit synchrony, which are physiological correlates of tinnitus in a majority of patients. Through empirical means, they found that bimodal (but not unimodal) stimulation produced long-term depression in the dorsal cochlear nucleus in guinea pigs. The stimulus method consists of sound stimuli, delivered by insert earphones, and somatosensory stimuli, delivered by electrodes placed on the skin of the cervical spine or cheek. The auditory stimulus was based on the individual subject's tinnitus spectrum and audiogram. The electrical (somatosensory) signal was timed to have a specific temporal relationship with the auditory signals (again, based on empirical findings in the guinea pig model). The device was designed for home use, thus facilitating daily, 30-minute treatment sessions for two, 4-week sessions (with a gap) before being crossed over to the opposite treatment arm (active or placebo). Ten of the twenty human subjects had clinically significant reductions in their tinnitus scores. This study is a fascinating example of the use of two forms of sensory neuromodulation in an interactive protocol. The availability of a well-developed animal model allowed for specific hypotheses about the mechanism of action to be developed. Since tinnitus is a sensory processing disorder, its alignment with a sensory neuromodulation approach is logical.

Bellesi et al. (2014) evaluated the possibility of enhancing slow-wave sleep (during non-REM sleep) using acoustic stimulation. The authors first evaluate the literature addressing the use of transcranial direct current stimulation (tDCS) and TMS, concluding that these methods are, at present, impractical. They target modulation of a peripheral evoked slow wave (K-complex) using entrainment via auditory stimulation. They list parameters of relevance for acoustic stimulation: intensity, frequency, timing (with respect to the onset of slow wave sleep) and entrainment. The latter parameter is not independent of the others and instead speaks to the goal of matching the acoustic stimulus frequency to that of an endogenous oscillator. Acoustic stimulation at 0.8 Hz fits with the EEG power band of 0.5-1.0 Hz associated with slow-wave sleep and has resulted in higher intensity, suggesting entrainment of what is thought to be a spontaneous thalamocortical oscillation. A remaining challenge for this approach is to time the administration of the acoustic stimulus, since stimulation at the wrong time in the sleep cycle can actually have an arousal effect. The authors suggest the use of ambulatory EEG to assess the proper time for administration, but this requirement calls into question the practicality of the method.

Somatosensory neuromodulation is a challenging format to assess since the receptive organ can be the entire surface of the body. Wildenberg et al. (2010) take a novel approach and use the tongue for the introduction of stimulation via an array of contact electrodes (PONS device - portable neuromodulation stimulator). One significant advantage of this approach is that the wet, salty surface of the tongue provides a low electrical input impedance, obviating the need for cleaning the skin and applying electrode gels, as is common with transcutaneous current techniques. The tongue also has a high density of somatosensory receptors, as can be seen in images of the somatosensory homunculus, originally created by Penfield (Schott, 1993). The authors assert that tongue stimulation results in less non-specific brain activation as compared with other NIBS approaches. In Wildenberg et al. (2011), the authors used BOLD MRI to infer that tongue stimulation results in pontine neuromodulation, via the trigeminal nerve, and it interfaces with the balance-processing network. This non-intuitive discovery underlies the clinical focus of the tongue stimulator for balance disorders.

The PONS device has been used in an RCT to assess efficacy for chronic balance deficits resulting from mild-to-moderate TBI (traumatic brain injury). Though not yet in peer-reviewed, published form, reported results are positive for a high-frequency stimulation arm (75.4% of subjects met the targeted improvement in SOT [sensory organization test] scores). The study sham, delivering a low-frequency stimulation, also proved to be efficacious and thus the primary endpoint was not met. This is an ongoing challenge with non-invasive neuromodulation studies in general: reproduction of a comparable procedural experience for sham-arm subjects as compared with active-arm subjects. Wildenberg at al. (2013) hypothesized that the afferent output from tongue stimulation enters the brainstem in proximity to the vestibular and trigeminal nuclei, moving upwards to the cortex, and is able to influence cortical processing of visual motion. Leonard et al. (2017) undertook an imaging study with multiple sclerosis subjects to assess effects of PONS stimulation over a 14-week treatment period. They found evidence of improved motor performance in active-arm subjects, as judged by BOLD MRI data localized to the motor cortex, suggestive of a neuroplastic change (specifically, the changes were durable enough to be subsequently recorded with fMRI). Of relevance here is that the mechanism of action of the PONS device seems to involve extensive pathways, accessed via a sensory input channel, albeit an indirect one via the tongue, and that there is evidence of durable neuroplastic change with beneficial effects for subjects (without significant device-related adverse events). A crucial observation is that this approach to sensory neuromodulation enables stimulation of brainstem regions. But the modulatory effects progress up from the brainstem to areas including the visual cortex and parieto-insular vestibular cortex (Wildenberg, 2013). And, importantly, the modulation signal follows endogenous sensory pathways.

We now turn to vestibular neuromodulation (VNM) and argue that this often-neglected sensory channel presents what is perhaps the best conduit for sensory neuromodulation. Caloric vestibular stimulation (CVS) is a widely used diagnostic technique, in particular for the study of balance disorders, and was initially explained by Barany (1911). The Fitzgerald-Hallpike (Fitzgerald & Hallpike, 1942) protocol for CVS is used routinely in the diagnosis of vestibular disorders. Galvanic vestibular stimulation (GVS) is a transcranial current method with the specific intent of creating a voltage bias across the two sets of vestibular organs by placing electrodes on the mastoid bone behind the ears (Fitzpatrick & Day, 2004). CVS and GVS, along with rotational methods, will be collectively referred to as vestibular neuromodulation (VNM).

The neuroscience of the vestibular system has been illuminated in extensive studies in animals and humans, but this rich literature is generally underappreciated by neurologists outside of audiological and balance related specialties (figure 5). Ayres (1972) book on the multi-sensory and integrative aspects of the vestibular system is a particularly cogent reference that illuminates the higher order cognitive elements of vestibular processing, going well beyond the study of balance.

Klingner et al. (2012) reported on an independent component analysis of vestibular cortical function. Using BOLD (blood oxygen level dependent) responses as markers of activity, seven different temporally defined components in the image data were identified. Four of these components were reported with a positive BOLD response. The authors stated that those components comprised the insula and retroinsular/parietal regions, the inferior/middle frontal gyrus, the superior temporal gyrus, the temporoparietal cortex, the parahippocampal gyrus, the

hippocampus and the cerebellum. Three components were mainly characterized by negative deflections of the BOLD signal: the pre- and postcentral gyrus, the anterior cingulate gyrus, the precuneus, the occipital lobe, and the supplementary motor area.

Lopez & Blanke (2011) reviewed the extensive literature around the structures and pathways comprising the thalamocortical vestibular system. The authors concluded that there is no unique and well-defined primary vestibular cortex comparable to primary sensory cortex for vision, somatosensation, and audition. The vestibular system is often referred to as a multi-sensory sense since it has direct or indirect projections into all cortical regions and vestibular sensory flow impacts the interpretation of other sensory modalities in the brain. And thus in addition to mediating balance, emerging evidence suggests that the vestibular network expands into dimensions of emotional processing, mental health and social cognition (Lopez, 2016).

Hitier et al. (2014) addressed the role of vestibular pathways in cognition, focusing on five major pathways that transmit vestibular sensory information to the distributed vestibular cortex: 1) vestibulo-thalamocortical; 2) dorsal tegmental nucleus via the lateral mammillary nucleus; 3) nucleus reticularis pontis oralis; 4) via the cerebellum; and 5) (hypothesized) via the basal ganglia. The cerebellum evolved from the vestibular and trigeminal nuclei (Bishop, 1959) and thus has a key role in processing vestibular sensory flow.

The cerebellum has, in the past, been relegated to a role in motor function, much as the vestibular system was viewed as being only relevant for balance. That view has now shifted to a more complete appreciation of this structure that contains four-times more neurons than the neocortex (Barton & Venditti, 2014). The cerebellum coordinates limb movement, controls movement-related sensory data acquisition, the timing of sensory acquisition and the prediction of the sensory consequences of action (Manto, et al., 2012). The cerebellum works with the vestibular system to interpret sensory inputs, creating forward models so as to enable reactions to changes in the environment (Sultan et al., 2012).

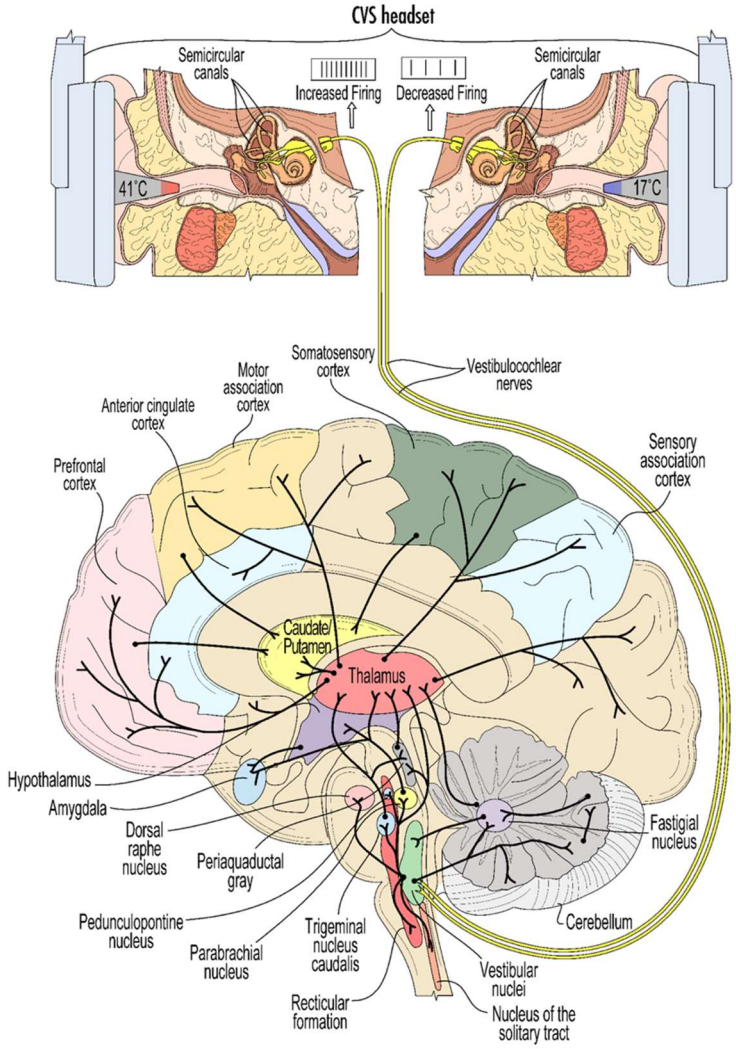


*Figure 5*: *A schematic view of some of the widespread connectivity of the vestibular system. The top panel illustrates the induction of CVS using warm/cool ear inserts (see figure 8 for example thermal waveforms). The 8th cranial nerve conveys vestibular stimulation to the vestibular nuclei in the brainstem.*

In summary, the vestibular system, and its distributed representation in the neocortex, presents a very appealing set of pathways for neuromodulation. There is not a major brain region, cortical or sub-cortical, that is not innervated by neuronal networks impacted by vestibular activity. And unlike with many other NIBS methods, the modulatory input is restricted to defined neuronal pathways. Also, as noted previously, innate processing of sensory signals enables distributed modulation within the context of local brain dynamics. As an example, Nishiike et al. (1996) found that irrigation based-CVS led to a reduction of the firing rate of the locus coeruleus (LC), whether the CVS increased or decreased the tonic firing rate of the vestibular hair cells. In other

words, modulation of the firing rate of the vestibular system was transformed and resulted in a wholly different firing pattern in the LC.

**Part 3: Models of disease of oscillators (clinical examples)**

Let us look at some specific examples where a neurological disease may be viewed as resulting from the dysfunction of oscillatory states and evaluate whether that perspective generates any new insights.

Epilepsy is often viewed simply as being characterized by hypersynchronous seizures, but the ictal and inter-ictal patterns of synchronization are more complicated than that. Muller et al. (2014) described varying degrees of synchronization prior to and during a seizure event. They described the peri-ictal evolution of brain network function as transitioning from a predominantly random topology to a more regular network and back again. They suggested that high synchronization at the end of a seizure is in fact a signature of the termination of the seizure. Yet throughout, they stated that there is a consistent trace of topology associated with the default mode network. In other words, the default organization is not lost during a seizure and ultimately reasserts itself. Perhaps counter-intuitively, epilepsy seems to be characterized by cortical regions that have poor connectivity and the hypersynchronous activity of a seizure works to re-integrate disconnected regions (Rummel et al., 2013; Schindler, private communication). Kusmierczak et al. (2105) addressed changes in local and long-range connectivity between cortical neurons as a component of the epileptogenic process after deafferentiation in an animal model. They found evidence that as axons started to reconnect the transected regions, the balance of long and short range excitatory connections altered neuronal excitability. It may be that a similar process occurs during post-traumatic epilepsy or that similar imbalances occur with idiopathic epilepsy. Is a seizure the brain's attempt to re-establish normal cortical connectivity?

Finding a biomarker for migraine onset is a current aim in headache research. Coppola et al. (2012) provided evidence that, interictally, migrainuers exhibit poor sensory habituation. Goadsby et al. (2017) argued that migraine headache is a disorder of sensory processing, which cycles based on development (genetics) and environment. They focused on abnormal brainstem function in the premonitory phase of a migraine, when the well-known sensory phobias emerge. Brighina et al. (2009) provided evidence that cerebellar inhibition is reduced in migraineurs and it is known that the cerebellum exerts inhibitory control on the cortex. Since the brainstem, cerebellum and cortex are all involved in sensory processing, a failure of habituation would seem to be a result of widespread network dysfunction. Interestingly, as the migraine develops, sensory habituation normalizes (Coppola et al., 2013). Is a migraine the brain's attempt to re-establish normal sensory sensitivity?

Motor dysfunction in Parkinson's disease (PD) results from neurodegeneration, most particularly in dopaminergic pathways involving the substantia nigra and striatum. de Hemptinne et al. (2015) described an elegant experiment undertaken with PD patients who had implanted DBS devices and who were undergoing invasive brain surgery. This allowed the authors to use electrocorticotography to measure cross correlations between activity in the gamma and beta bands. PD patients receive DBS implants to mitigate some movement disorder symptoms and it had been suspected that over-coupling between beta and gamma in the motor cortex increased with

severity of disease. Indeed, de Hemptinne et al. found that CFC increased with the DBS device turned off, and decreased when the device was active. How the neurodegenerative effects of PD altered the normal amount of CFC is not wholly clear, but this is a clear case whereby changes in normal brain oscillator function have a clear and measureable clinical consequence. As a consequence of neurodegeneration, the brain is not able to re-establish normal connectivity, but through artificial stimulation it is possible to reduce pathological CFC.

In these three examples, epilepsy, migraine and PD, we see that the diseases are characterized by widespread network dysfunction, which implies collective action of brain oscillators, if one accepts that healthy brain function is underpinned by collective oscillations. Taking an oscillator-centric viewpoint leads to a generalized way of understanding neurological diseases that are typically not considered together (though migraine and epilepsy are sometimes discussed jointly in terms of cortical spreading depression). Further, there is evidence for migraine and epilepsy that the brain acts to re-establish a more stable network configuration, but that allostatic drive seems to be associated with a seizure (in the case of epilepsy) or a migraine and therefore the brain's response seems associated with the signal pathologies of the diseases. The use of DBS for motor dysfunction in PD suggests that direct alteration of aberrant oscillatory states can be therapeutic and we shall argue that sensory neuromodulation is particularly well-suited as a therapeutic methodology in this regard.

**Part 4: What keeps oscillators functional?**

Adult neurogenesis may occur to a limited degree in the hippocampal complex (Anacker & Hen, 2017), but changes in existing neuronal structures in the adult brain are largely the result of neuroplastic alterations in networks; in synaptic connectivity. Adult learned behavior and memory formation can only occur through synaptic modification. Alterations in connectivity as a result of stroke have historically provided a significant source of understanding about how function is enabled by specific brain regions (Hallett, 2005). One particular observation with stroke patients provides an interesting conceptual model for functional loss more generally. An idling neuron (Neubauer et al., 1992) is a term that was coined to describe a neuron found in an ischemic penumbra with a living soma, but with a reduced dendritic arbor or overall reduced metabolism. The idling neuron is not dead, but it is not part of a network and therefore not functional. Within this model, early stroke intervention improves the likelihood of re-integration of the idling neuron into a functionally useful configuration. One can see an analogy with neurodegenerative disease, where a neuron may be disconnected, but still alive. More generally, what innate processes maintain neural networks that underpin oscillatory brain states?

What keeps oscillators from failing or drifting to a new configuration? The extensive studies of the default mode network (DMN) bear on this question (Fox & Raichle, 2007; Raichel, 2015), but the answer is still unclear. Clearly the "default" mode must be a stable configuration upon which intentional, task-positive functioning relies and thus should be resilient to perturbation or damage (Dosenbach et al., 2007). Pinal et al. (2015) considered age-related changes in the DMN by studying brain oscillatory activity in healthy young and old adults during a visual task. They found that whereas an age-related loss of synchronization occurred in executing the task, the default mode maintained synchronous activity, which they aptly describe as being stuck in the default mode. Aerobic fitness is consistently associated with the maintenance of optimal brain function. Talukdar et al. (2017) examined the brain connectome of healthy young adults, citing enhanced

neuroplasticity in specific targeted regions. They found the benefits of aerobic exercise were indeed widespread, suggesting a primary causal relationship, but the study was not designed to speak directly to mechanism of action. The role of sleep in maintaining stable brain networks is a subject of intensive study. Larson-Prior et al. (2009) concluded that the spontaneous BOLD MRI activity seen in the descent to sleep reflect processes that maintain functional integrity of the brain. They went on to note that even under general anesthesia, default functional connectivity remains intact. (If this were not the case, how would the patient re-emerge from anesthesia with an intact mind?) The synaptic homeostasis hypothesis (SHY; Tononi & Cirelli, 2006) posits that synaptic strength weakens during sleep in order to, conceptually, preserve important neuronal connections and winnow out unimportant ones. This must obviously occur while maintaining the DMN and in fact evidence supports the importance of sleep for proper DMN function (Gujar et al., 2010).

Chan et al. (2016) considered correlates between neuronal oscillations and mitochondrial dysfunction. In this case, the authors focused on the disruption of cortical oscillators due to weakness of the neurons comprising those oscillators, resulting from metabolic stress via mitochondrial damage. The authors looked at a number of examples of diseases for which this linkage could have diagnostic and therapeutic import. We now return to the idea that changes in baseline oscillator function may trigger innate neuroprotective responses. Might the brain use changes in oscillators to trigger biochemical responses that work to fix dysfunctional oscillators?

The Torres-Aleman group has proposed a compelling hypothesis that links oscillatory brain activity to the maintenance of the neurons that comprise such oscillators. We list some of the findings and predictions associated with this hypothesis as a preliminary to exploring how sensory neuromodulation might co-opt a natural process for maintaining the integrity of neural network function. In Nishijima et al. (2010), the authors detailed a pathway by which IGF-1 (insulin-like growth factor) enters the CNS (central nervous system) from systemic circulation in response to the activity of neural oscillators (figure 6). IGF-1 is a very well-studied neurotrophic biomolecule that has been impressively stable across evolutionary time. It is reported to improve resistance to mitochondrial apoptosis (Akundi et al., 2012; Gu et al., 2004; Kang et al., 2003) and promote synaptogenesis (Nieto-Estevez et al., 2016). However, just increasing IGF-1 levels can lead to negative consequences for cell viability (Bitto et al., 2010). Therefore, for IGF-1 to be effective as a neuroprotective agent, it must be supplied when needed in response to neuronal activity or stress. Nishijima et al. (2010) showed that the activated process by which IGF-1 crosses the blood-brain-barrier (BBB) is frequency dependent, suggesting that this pathway evolved to support and maintain baseline neuronal dynamics. They hypothesize that the proneurogenic effects of epilepsy, some forms of external neural stimulation, and exercise may all depend to some degree on activated transport of IGF-1 through the BBB. Nishijima et al. (2016) expanded the model of IGF-1 transport and emphasize that uptake is dependent on cerebrovascular availability of IGF-1 to cross the BBB. Since exercise is understood to improve cerebrovascular blood flow (CBF), there is a direct link to enhancement of IGF-1 uptake.

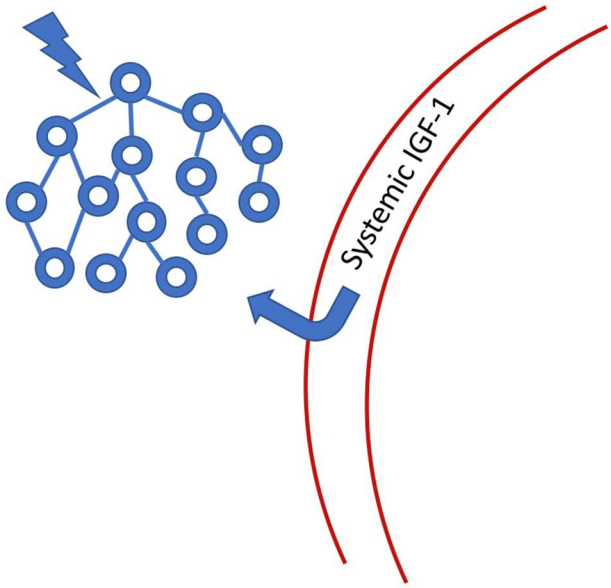


*Figure 6: Systemic IGF-1 is transported through the blood-brain-barrier to the site of neuronal activity. IGF-1 binding protein is cleaved from the IGF-1 molecule, allowing passage through the barrier. Once in the CNS, IGF-1 has a limited half-life because it no longer has its binding protein chaperone. See Nishijima et al., 2016 for a more detailed figure.*

We therefore see that the maintenance of stable oscillatory states in the brain is essential to proper function over time and this reality suggests that there are innate response mechanisms that support this stability. That neuronal dynamics regulate the transport of IGF-1 through the BBB provides a specific example of how a neurotrophic biochemical response acts to support neuronal health and function. Toth et al. (2015) reported on the disruption of neurovascular coupling in a murine model resulting from IGF-1 deficiency, emphasizing the integrative role of neuronal activity and the metabolic function mediated by the vasculature.

**Part 5: Details for One Form of Sensory Neuromodulation**

The Hebbian doctrine often summarized as "neurons that fire together, wire together," is not prescriptive about the functional impact of that new wiring. When applying artificial neuromodulation to a neuronal network, with the aim of altering synaptic connections, why would the effect be beneficial, versus neutral or negative? DBS is often very effective for movement disorders, but there are reports of negative effects on verbal fluency (Wojtecki, 2006) and the onset of urinary incontinence (Aviles-Olmos, 2011), underscoring the incomplete understanding of how DBS affects brain regions outside of the immediate electrode placement location (Hariz, 2017). When considering NIBS, as discussed earlier, interfacing to the regional neuronal dynamics with a single excitation source is not possible and so focus has been on disrupting regional activity or attempting to entrain at a specific frequency. Since too much cortical synchrony is also associated with loss of consciousness or seizures, widespread entrainment into a single dynamic state presents

risks. It is interesting to note that NREM was once called synchronous sleep, reflective of the dominant activity seen on EEG recordings.

Sensory neuromodulation delivers a signal, even if it is non-physiological, via an innate network that processes the artificial signal just as it would naturally occurring sensory stimuli. We propose, therefore, that sensory neuromodulation may act to encourage developmentally established network behavior and thus may act to strengthen endogenous oscillators that couple to the sensory network. In other words, the sensory traffic drives target oscillators in a manner consistent with innate function. We hypothesize that sensory neuromodulation might then act to rehabilitate dysfunctional neural networks, bringing them back closer to a developmental state via neuroplastic modification (figure 7). Evidence for such rehabilitative potential for sensory neuromodulation is not definitive, but we now review some clinical results that support this hypothesis.

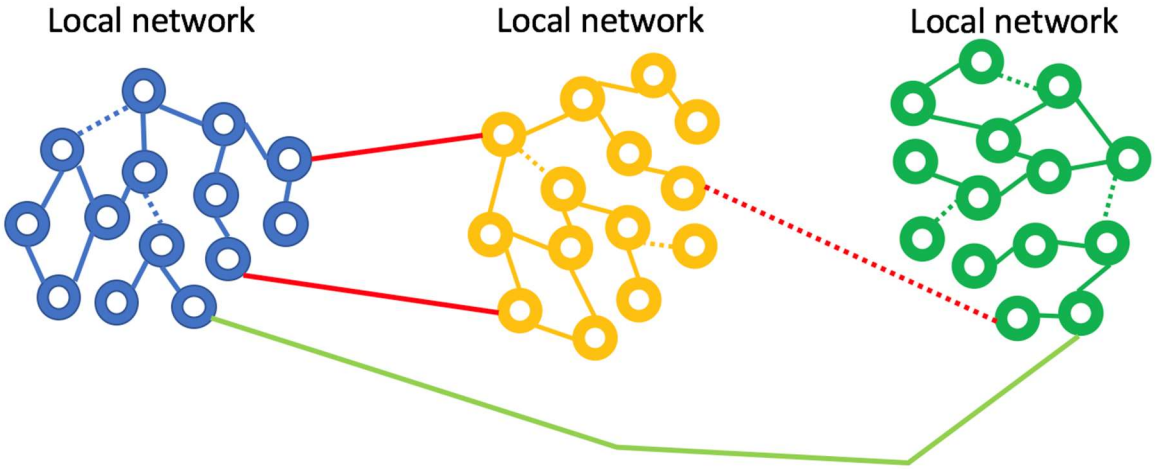


*Figure 7: Neurological disease represented as weak or broken network connections. Sensory neuromodulation is hypothesized to force activity in weak networks, strengthening synapses and improving coupling. The IGF-1 mechanism may be a key player in this network repair process.*

VNM:

CVS has been used diagnostically for decades, and there have been a number of small studies using CVS in a therapeutic context (e.g., Grabherr et al., 2015; Kolev, 1990; Rode et al., 2002; McGeoch et al., 2008; McGeoch et al., 2009), but diagnostic-style CVS devices, which use water or air to flood the ear canal, are not amenable to home use. Current GVS devices are also not easily adapted for home use because of the need to clean the skin carefully, apply a conductive gel, and affix electrodes over the mastoid bones behind the ears, but an even larger body of work exploring potential clinical applications of GVS exists (e.g., Cai et al., 2018; Hwang et al., 2016; Kataoka et al., 2016; Kerkhoff et al., 2011; Kim et al., 2013; Okada et al., 2015; Pal et al., 2009; Pan et al., 2008; Samoudi et al., 2014; Wilkinson et al., 2014; Yamamoto et al., 2005). The past work with diagnostic-style CVS and research-style GVS devices should be viewed as purely research driven or pre-clinical. No regulatory clearances have been obtained for these devices in a therapeutic context. The ability to conduct longitudinal VNM therapy seems necessary to achieve sustained clinical efficacy and having a home-use device format is the only tractable approach to enable chronic therapy.

Rogers & Smith (US 8,262,717) conceived of a solid-state CVS device that would warm and cool the ear canal, thus enabling longitudinal therapy in the home. In order to extend treatment times with CVS, a time-varying thermal stimulus is needed to avoid adaptation of the vestibular hair cells (Bock et al., 1979) and so the solid-state CVS device was equipped with the means to deliver time-varying thermal waveforms, independently to both ears (figure 8). CVS alters the tonic firing rate, of ~100 Hz, of the regularly firing vestibular hair cells. Applying a triangular temperature waveform (fig. 8) results in a time-varying firing pattern in the vestibular hair cells around the 100 Hz tonic rate. Additionally, the envelope of the triangular waveform establishes a slower modulation and when both ears are stimulated simultaneously, at different frequencies, the resulting afferent firing pattern reaching the vestibular nuclei can be quite complex and spans frequencies from 0.01 Hz to 100+ Hz. Therefore, even though the time course of thermal transfer to the inner ear during CVS is slow, at least on the order of seconds, it is important to recognize that modulation of the equilibrium firing rate means that frequencies centered on 100 Hz are also present.

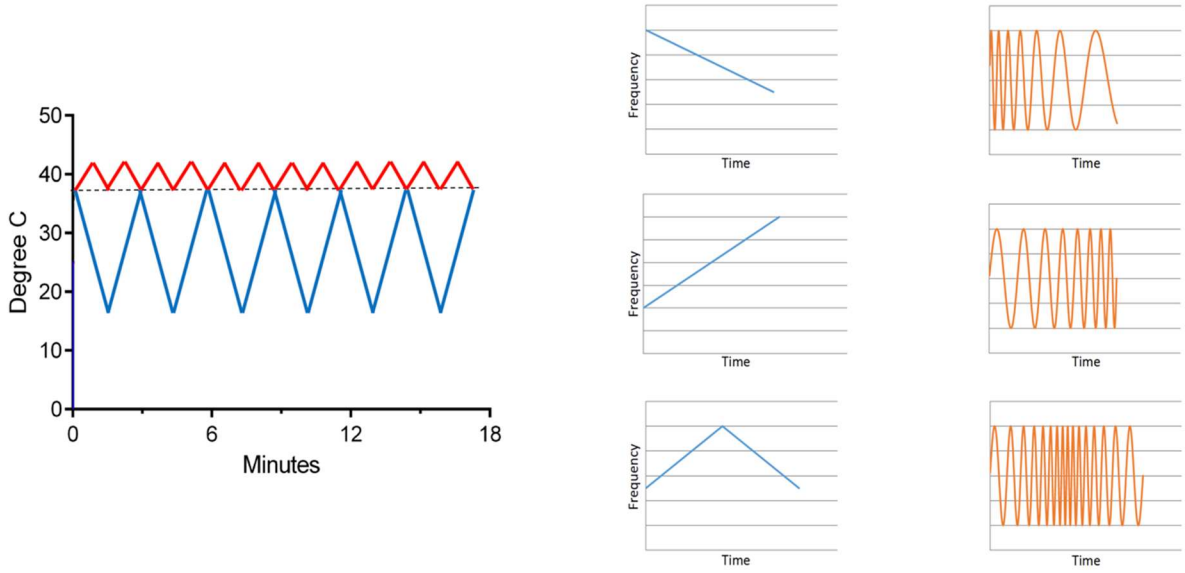


*Figure 8: An example of time varying waveforms used with the solid-state CVS device (left). One ear receives a warm triangle wave and the other a cold triangle wave. As seen in figure 5, warming increases the afferent firing rate and cooling decreases it. On the right, the effect of a time-varying temperature on the hair cell firing rate is shown graphically. The response (orange) frequency shifts in time, a phenomenon called a "chirp." Thus a complex range of firing rate modulations can be achieved.*

The vestibular neuroscience of migraine is explored in Black et al., 2018 (invited review, Headache Currents). Time-varying CVS demonstrated efficacy in reducing headache burden in episodic migraineurs (Wilkinson et al., 2017). Migraineurs used the CVS device on a daily basis, at home. Over a 3-month long treatment period, a per-protocol reduction of 3.9 migraine days relative to a baseline of 7.7 migraine days. A control group showed a 1.1-day reduction from a baseline of 6.9 days. Analysis indicated that blinding was effective. Subjects used up to one concurrent preventive drug and as-needed abortive drugs and so the gains with CVS device use were additive, likely due to a parallel mechanism of action. This device was recently cleared by the FDA for use in treating

episodic migraines.

The migraine study involved slow modulations in temperature, in the range of 0.008 – 0.033 Hz. The temperature changes then induce alterations in the firing rate of vestibular hair cells at the in the same range of frequencies. Is there any evidence that such slow oscillations might be important, on top of the basic need to avoid adaptation of the vestibular response? Black et al. (2016) provided evidence of entrainment of a pontine pacing center, which engendered oscillations in cerebral blood flow velocity, using time-varying CVS. In that study, the oscillations appeared to sharpen to what was presumably a natural resonance, at about 0.025 Hz, and persisted when CVS was stopped, a strong indicator of entrainment. Sliwka et al. (2001) reported that migraineurs had abnormal B wave activity (interictal), spontaneous oscillations in blood flow velocity in a range from 0.008 – 0.05 Hz. B waves are thought to originate in the pons and may be part of a the autoregulatory response (the B wave period is roughly the transit time of blood from the heart to the brain and back). Swlika et al. suggested that abnormal B wave activity in migraineurs may stem from a dysfunction in the monoaminergic/serotonergic system in the brainstem, a hypothesis that overlaps independent models of migraine pathogenesis (Coppola et al., 2009). Therefore, evidence for entrainment of B waves with time-varying CVS could be a biomarker of utility when seeking to titrate therapy for individual migraineurs.

Oscillations in the B wave frequency *range* have also been observed in BOLD MRI studies aimed at measuring cortical functional connectivity (Cordes et al., 2001; Bharath et al., 2017; Leopold et al., 2003; Schmidt, 2009) and appear in slow-wave sleep (Dang-Vu et al., 2008). Dang-Vu et al. suggested a possible relationship between the observed oscillations in slow-wave sleep and waking DMN, implying a restorative role of sleep on large-scale cortical functional organization. Oscillations in the B waves range during sleep have also been seen with EEG (Terzano et al., 1985) and with transcranial Dopper sonography in newborns (Ferrarri et al., 1994). Are the oscillations seen in functional connectivity studies related to those seen in cerebrovascular studies or is there just a coincidental overlap in frequency ranges? Even if the two phenomena don't share a common pontine pacing center, entraining one sets up the possibility of entraining the other. Measuring the onset and strength of entrainment of targeted brain oscillators presents a tangible method for the titration of therapy. No functional brain oscillator can remain isolated (uncoupled) from other oscillators (this is the essence of the small-world network concept) and time-varying CVS presents a powerful method for exciting *complete networks*, innervated by the vestibular system. Coupling occurs not just for oscillators that have the same resonant frequency, but cross-frequency coupling (CFC) allows for interactions between oscillators having different fundamental frequencies.

B waves might also be of interest in assessing the health of neurovascular coupling (NVC). NVC has gained interest amongst researchers as a key factor influencing the progression of neurodegenerative disease. Iadecola (2017) stated that maintaining neurovascular health promotes brain health and Lecrux & Hamel (2011) looked at Alzheimer's disease, in particular, in the context of alterations in neurovascular function. Toth et al. (2017) summarized the interplay between cerebral autoregulation, in which B waves play an important role, and NVC. The authors suggested that understanding vascular contributions to cognitive impairment and dementia has significant implications for preserving brain function in older individuals. Ozturk & Tan (2018) examined the evolution of cerebrovascular function and its support for the unique functionality of the human brain. Their work highlights the inevitability of the effects of neurovascular pathology

on cognition.

Time-varying CVS has also been used in a case study with two subjects in a minimally conscious state (Vanzan et al., 2017) with the aim of increasing awareness. Spontaneous recovery for these subjects generally occurs within a time window after emergence from coma and both of the subjects were past the time when natural recovery was expected. As measured with coma recovery scales (WHIM & CRS-R), improvement seemed to show a time-locked association with CVS treatment epochs, which consisted of 1-month of daily treatment, followed by 1-month of sham treatment, and ending with a second month of active treatment. Improvements were recorded during active treatment and no gains were seen during sham treatment. Note that the subjects were likely unaware of the active/sham changes. One of the subjects in particular demonstrated durable gains and progressed from an inability to move his gaze to a person in the room to initiating conversation and answering simple questions. The authors noted that the apparent gains imply improved function across a number of brain regions, but most particularly the thalamocortical projection system, and neuroplastic modification of neuronal pathways. They further suggested that vestibular pathways go well beyond a role in autonomic motor control and underlie higher cognitive states, a viewpoint consistent with the literature reviewed in Part 2.

As a final example of clinical results based on time-varying CVS therapy, we review work summarizing longitudinal therapy delivered to PD subjects. An initial case report (Wilkinson et al., 2016) found evidence of gains in several motor areas, with some evidence of durability past the end of treatment. That study was followed with a single-site RCT (Wilkinson et al., accepted) with the aim of measuring changes with both motor and non-motor scoring scales. All subjects were on dopamine replacement therapy (DRT) and treated daily for 2-months. They were evaluated in the "on" state (had recently taken their DRT medication). A blinding analysis concluded that subjects were unaware of whether they were in the active or placebo arm of the study. There are two general aspects of the study that stick out: broad efficacy across motor and non-motor symptoms and durability of gains for months after the end of treatment. When a DBS device is switched off, motor symptoms re-emerge almost immediately. There is no single drug that has shown efficacy for both motor and non-motor symptoms (Seppi et al., 2011). Figure 9 is derived from Wilkinson et al. (accepted), amalgamating graphs from a number of different measures into one semi-quantitative graph. The same general shape appears, suggesting a slow return to baseline over a timeframe that seems too long to be explained by changes in up/down regulation typically seen in receptor binding kinetics (Zhuang et al., 2013). If the data are representative and if this result can be reproduced in a larger, multi-site RCT, then the most likely explanation is that multiple neuronal pathways were improved by the use of time-varying CVS, through neuroplastic modification.

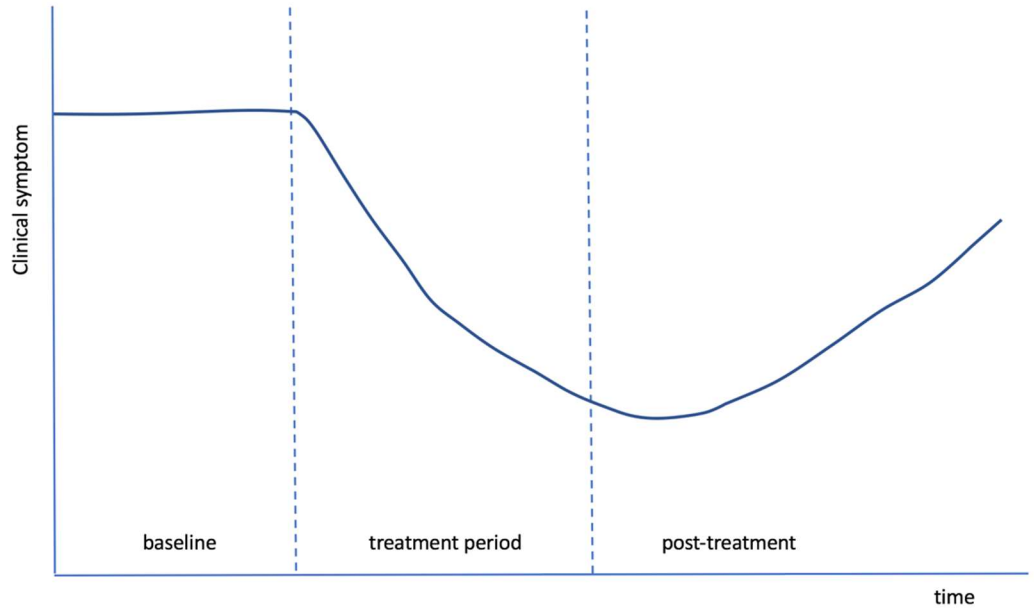


*Figure 9: A composite graph of the response, over time, of multiple, different symptoms in Wilkinson et al. (accepted). The same characteristic shape and time course was seen across independent measures, suggesting a common effect, most likely neuroplastic modification of the dysfunctional pathways associated with the various symptoms.*

**Part 6: Discussion and future questions**

We have reviewed the evidence supporting the contention that brain function is enabled by oscillatory activity of neuronal networks, at both local and global scales, and that these developmentally established oscillatory networks are actively maintained to ensure proper brain function. Therefore, one can propose a model of neurological disease based on specific changes in oscillatory networks. Using neuromodulation, via implanted or non-invasive means, to alter, and ideally correct, aberrant oscillation patterns is a compelling translational goal. We propose that sensory neuromodulation, defined as the use of endogenous sensory networks to deliver a neuromodulatory signal to the brain, is categorically different from the way in which other current neuromodulation devices operate, as they deliver stimulation via implanted electrodes or diffuse electric field pathways established with externally placed electrodes or via current induction with rapidly changing magnetic fields. Sensory neuromodulation is intrinsically extensive in reach and thus acts to modulate multiple oscillators systems in parallel and the modulation signal is transformed to be consistent with local neuronal oscillator dynamics. We suggest that modulating many brain oscillators in parallel is important for the clinical end goal of altering and improving network function. We have provided one specific example from the literature of how oscillator signaling can trigger biochemical responses via IGF-1, which acts to protect neurons and facilitate network function. Admittedly, sensory neuromodulation is in the early days of development, but there is already growing clinical evidence that it may have multi-faceted impacts on disease symptoms that is quite different from the generally narrow focus of pharmaceutical targeting (Drews, 2000), where the concern is to avoid non-specific targeting and adverse events. Much of our focus has been on time-varying CVS, based on the authors' direct experience with the method,

but also because the vestibular sensory network is so well-suited to the task of delivering neuromodulation throughout the brain.

At present, the way in which sensory neuromodulation works, and how well it works, is not fully established and more clinical studies and mechanism of action studies are required. Yet it is reasonable to hypothesize, using the oscillator model of neurological disease, about what to expect.

*Why it helps and doesn't hurt*

An oscillator-centric model clarifies how sensory neuromodulation can in principal work broadly and may mitigate multiple disease symptoms. This is because the nature of networked oscillators is to enable cross coupling between individual oscillators and networks. As an illustrative example, consider the cardiac oscillator. Heart rate variability (HRV) is a measure of the ability of the heart to respond to changes in demand from the body. High HRV means that the heart is very adaptive and is associated with good health. Low HRV means that the heart is not adaptive and means that the cardiac oscillator system is too weakly coupled to other brain-driven oscillator networks. If an oscillator is too weakly coupled, it is ineffective and thus the interventional goal is to improve and increase coupling to a normal level. In the case of the cardiac oscillator, exercise and a healthful lifestyle are well accepted as improving cardiac function, improving HRV (Kiviniemi et al., 2010). Aerobic exercise encourages the heart to be rate adaptive and we submit that forcing the cardiac oscillator to be responsive to the demands of the body is achieved by exposing it to an appropriately stressful stimulus. Conversely, inactivity places low demands on HRV and the cardiac oscillator will become more weakly coupled to the body. The cardiac oscillator has a developmentally established level of coupling to the body, but the strength of coupling can change: it can improve via exercise or it can decline via inactivity. We assert that beneficial coupling is encouraged by forcing a target oscillator to work with other network oscillators and coupling is altered (figure 7) through synaptic modification (neuroplasticity). This realization has important consequences for therapeutic intervention. Firstly, it's not possible to harm the function of a target oscillator by entraining it with other oscillatory networks for, indeed, entrainment is fundamental to its function. Thus oscillator entrainment by sensory neuromodulation will not interfere with normal function. The stimulus does not need to be focused only on a damaged region, for instance. Secondly, entrainment works to reinforce the integrity of an oscillatory network's developmentally derived form. Sensory neuromodulation provides input through endogenous channels and thereby forces functional responses, which reinforce synaptic coupling, in those areas innervated by the sensory pathways. It is for this reason that the extensive innervation of the vestibular network recommends it as a preferred conduit for sensory neuromodulation therapy. Understanding how sensory neuromodulation should work to maintain and improve coupling between oscillators would lead to the expectation of extensive effects on function (and thus potentially the mitigation of multiple disease symptoms) and durability of gains (because the effect is to create neuroplastic modification of the coupling between oscillators).

The picture is not as simple as the one discussed above. If a neural network is disrupted by trauma or a neurodegenerative disease, then one can posit that the goal of sensory neuromodulation therapy is to re-established the pre-trauma, pre-disease configuration. The assumption is that the developmentally established network configuration is a preferred baseline to which the system seeks to return. But what about a disease that results in developmental abnormalities? In that case, there is no normative configuration to which to return. And diseases that have a strong behavioral

component may not be amenable to therapy alone without some form of physical or cognitive behavioral therapy. Let us look at each of these three examples in turn.

A neurodegenerative disease (like PD) or disease that is trauma-induced (like TBI or stroke) results in an alteration in pre-disease oscillatory networks. Early evidence from Wilkinson et al. (accepted) suggested that there may be a plastic response to time-varying CVS that works to return function broadly. It may be that concommitant physical training could help with motor dysfunction, in particular, and this would result in a ratchet effect whereby neuromodulation improves function and physical therapy improves function further. Studies with the PONS device typically included a physical training component (Chisholm et al., 2014). An interesting question for future research is whether sensory neuromodulation creates neuroplastic facilitation that augments conventional physical therapy.

Diseases like schizophrenia and idiopathic migraine are developmental. If there is no disease-free baseline to which to return, what does this mean for the applicability of sensory neuromodulation? Gerretsen et al. (2017) used irrigation-based CVS with schizophrenia subjects and found evidence of transiently improved insight to illness. The authors concluded that, similar to hemispatial neglect, CVS acted to balance activity in the two hemispheres, making use of the potential of unilateral CVS to preferentially activate one hemisphere. This is an interesting example as it points out the spectral nature of diseases like schizophrenia where improvement in one symptom may still have an impact on patient outcomes. Wilkinson et al. (2017) offered clear evidence of benefit from time-varying CVS for idiopathic episodic migraine. Why this is so is unknown, but we noted earlier that the brain actually does try to re-establish normal sensory habituation during an attack. And so perhaps a helpful viewpoint would be to think of the migraine brain as having two states, habituating and non-habituating, and neuromodulation increases the prevalence of habituation, thus reducing the sensory dysfunction that may be the source of the disease (Goadsby et al., 2017).

For behaviorally driven diseases like type-II diabetes and addiction, it seems unlikely that neuromodulation alone can't be effective since habits and lifestyle must also be adjusted. The aim, rather, for neuromodulation could be to make the adoption of lifestyle changes easier and to help to establish new habitual patterns.

Another challenge for sensory neuromodulation is how best to titrate therapy for a given individual. To meet this challenge, the establishment of suitable biomarkers would be helpful. As one example, EEG provides a measure of pernicious CFC in motor symptoms of PD (de Hemptinne et al., 2015). TCD revealed that time-varying CVS (and not constant temperature CVS) created cerebral blood flow velocity oscillations, possibly providing a target of relevance for migraines (Black et al., 2016). Functional imaging studies do not lend themselves to routine application for individual patients, but general lessons can be learned about how best to deliver sensory neuromodulation (Wildenberg et al., 2013). It may be possible to use inexpensive and non-invasive methods, like heart-rate variability, as a proxy for more elaborate procedures once the relevant parameters are identified. Looking for evidence of entrainment of a target seems like a fertile place to start. Ultimately, as we learn more about the mechanisms of action of sensory neuromodulation, we will understand better how to titrate therapy more effectively.

**Part 7: Conclusion**

The advent of home-use, low risk devices for delivering sensory neuromodulation creates a distinct advantage in that such therapies can be used early in the progress of a disease, versus implanted devices that are relegated to late-stage disease. This potential meshes with current efforts to detect neurodegenerative disease at an early stage, via the use of biomarkers. Taking therapeutic action simply on the basis of genetic profiling is a challenging decision, ethically, however a low-risk, low side-effect therapy mitigates the downside of acting early.

The brain, viewed from an engineer's context, is energy intensive (consuming some 20% of metabolic output in about 2% of body mass) and is comprised of irreplaceable parts (no extensive adult neurogenesis). That leads to a poor prognosis for long-term function, unless innate support and repair mechanisms are in place. The challenge is different for organs that do generate new cells. Autoregulation is clearly one mechanism that supports brain function. The clearance of waste products, by the circulatory system and lymphatic and glymphatic routes, is also important. We find that the IGF-1 model proposed by Nishijima et al. (2010) presents a new avenue for model building, linking brain oscillators to underlying biochemical pathways that help to facilitate neuroprotection.

Viewing neurological disease in terms of dysfunctional oscillators enforces a systemic viewpoint since all brain oscillators are ultimately connected to each other. Further, one can create a chain of reasoning by which the maintenance of default oscillatory dynamics is the guiding force that mediates underlying biochemical responses that work to instantiate innate neuroprotection. We suggest that neuromodulation via a sensory organ is a particularly attractive approach by which to support proper functioning of neuronal oscillator networks.

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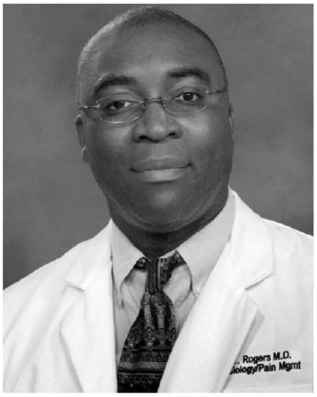


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Appendix:

It is hard to overestimate the ubiquity of IGF-1 in metabolic processes. These references provide an illustrative, though very incomplete, overview: Sharma et al., 2016 and Ebert et al., 2008 [IGF-1, glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF)]; Ng & Tang, 2013 [IGF-1 & sirtuin 1 (Sirt1)]; Barbieri et al., 2009 [IGF-1 & telomere length]; Ayadi et al., 2016 [IGF-1 & neuroprotection of striatum]; D'Mello et al., 1997 and Suzuki et al., 1998 [IGF-1 & inhibition of apoptosis]; Sonntag et al., 2013 [IGF-1 & cerebrovascular aging]; Zheng et al., 2004 [IGF-1 & brain-derived neurotrophic factor (BDNF)]; Gontier et al., 2015 [IGF-1 and amyloid-beta]; Tran et al., 2014 [IGF-1 & cellular senescence]; Grinberg et al., 2013 [IGF-1, tumor necrosis factor-alpha (TNF-α), and oxidative stress]; Robida-Stubbs et al., 2012 [IGF-1 and target of rapamycin (TOR)]; Mason et al., 2001 [IGF-1 & interleukin-1β].) In terms of IGF-1's role in disease progression, a small listing of studies of interest: Sung et al., 2014 [IGF-1 and amyloid beta in Alzheimer's disease]; Grinberg et al., 2017 [IGF-1 inhibits cortical spreading depression]; Trueba-Saiz et al., 2013 [loss of serum IGF-1 as early biomarker of AD]; Major & Jarquin-Valdivia, 2018 [disruption of IGF-1 homeostasis leads to neurodegenerative disease]; Yang et al., 2018 [IGF-1 signaling in Parkinson's disease]; Aberg et al., 2006 [IGF-1 and neuroprotection in the adult brain]; Pitt et al., 2017 [IGF-1 and synaptopathy]; Levine et al., 2012 [IGF-1 and signal transduction in PD]; Sonntag et al., 2013 [IGF-1 and cerebrovascular aging]

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