Neurofeedback Training for Parkinsonian Tremor and Bradykinesia

by

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A Paper Presented to the

Faculty of Mount Holyoke College in

Partial Fulfillment of the Requirements for

the Degree of Bachelors of Arts with

Honor

Department of Biological Sciences

South Hadley, MA 01075

May, 2006

This paper was prepared
under the direction of
Professor Sue Barry
for eight credits.

ACKNOWLEDGMENTS

I would like to express my deepest appreciation and gratitude first and foremost to professor Sue Barry, without whom this thesis would not have been possible. Thanks also to Dean Bowie and Professor Joseph Cohen for their help, encouragement and time. This study was enabled by support and funding from Struthers Parkinson's Center, and a large thank you goes to Catherine Wielinksi, for making this happen. I am also indebted to Nancy Lech and the Mount Holyoke College biology department for all of their patience and support.

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ABSTRACT

In his work on the spinal cord, Grahm Brown demonstrated that locomotion is largely mediated by spontaneous, intrinsic activity within neural circuits (1919). While the greater biomedical community – which instead emphasizes the contingency of behavior on sensory stimuli – has largely ignored this, attentions are beginning to shift as remarkable clinical results are being achieved by therapies grounded on Brown's tenet. One of the most promising is neurofeedback, a type of EEG biofeedback that allows one to manipulate one's brain wave activity if offered feedback on it, training whatever changes correlate with symptom alleviation into long-term improvement through operant conditioning. It has encountered great success alleviating symptomology in a wide variety of conditions, but its mechanism remains unknown and efforts for its pursuit largely unsupported.

Much support for the therapy can be drawn from the research of Rudolfo Llinas and colleagues in their work on thalamocortical dynamics. They demonstrated the presence of slow-wave theta activity within the brains of patients diagnosed with Parkinson's disease and detailed the neurophysiological relationship between the abnormal rhythmicity and parkinsonian tremor and bradykinesia. Llinas's theory agree very well with what is known about the science behind deep brain stimulation, a widely-used therapy for movement disorders that effectively alters the aberrant rhythmicity. Neurofeedback practitioners claim to have success utilizing a protocol that targets similar activity, but there have yet to be any studies examining this.

As a practical application of this theory, a pilot study on the effects of neurofeedback on Parkinson's disease is proposed here, which will be conducted in the following months. Not only may symptom alleviation result for the benefit for the person with PD, but in validating a theory that relies on a differing foundational premise than that which is currently prevailing in biomedicine may offer insight into the functional organization of the nervous system.

COMMONLY USED ABBREVIATIONS

DA: Dopamine

EEG: Electroencephalograph

Gp: Globus Pallidus

MEG: Magnetencephalography

PD: Parkinson's disease

RE: Reticular neurons

SMR: Sensorimotor rhythm

TC: Thalamocotical

TCD: Thalamocortical dysrhythmia

TCR: Thalamocortical rhythmicity

TLR: Thalamocortical neurons

VLa: Ventrolateral nucleus (anterior portion)

INTRODUCTION

Within the Jamesian theory of reflex, the nervous system is seen as a complex set of neuronal pathways triggered into action by external sensory stimuli (Finger, 1994). Support leading to the widespread acceptance of this view came from Sir Charles Sherrington's physiological experimentation on the spinal cord in the early 20th century. He claimed it to operate on a fundamental level by a set of complex reflexes, thus emphasizing the functional importance of sensory information in mediating behavior (Sherrington, 1915). This contrasted, however, with work being done around the same time by Graham Brown, who demonstrated that locomotion was still supported after complete dorsal root deafferentation (total removal of sensory input) of the spinal cord (Brown, 1914). Based on this, Grahm proposed that spinal cord function was mostly organized as intrinsically generated neuronal activity and described the motor output required for locomotion as a property of the spontaneous activity of the neuronal circuits in the spinal cord and brain stem.

This intrinsic activity is believed to be a reflection of the rhythmic generators found not just within the spinal cord and brain stem, but also throughout the brain. The functional importance of the intrinsic activity is not to be taken for granted, as Graham's study should show, but has in fact been ignored by the greater scientific community which has instead long sided with Sherrington's view. Indeed, these rhythmic generators are thought to be the

machinery of a self-regulatory control system that innovative therapies are acting to manipulate, achieving remarkable results in doing so.

One of the most promising is neurofeedback training, a type of EEG biofeedback that allows one to manipulate one's brain wave activity if offered feedback on it, training whatever changes correlate with symptom alleviation into long-term improvement through operant conditioning. It has encountered great success in treating a wide variety of conditions; from ADHD and epilepsy to mood disorders and organic brain injuries. Due to its categorization within alternative medicine, however, funding to conduct the necessary controlled studies with large-subject populations has been scarce.

The primary reason it has been categorized as such is because of its reliance on a model that differs fundamentally from that which currently prevails in the biomedical community. Neurofeedback training rests on what is called the model of disregulation, and its emphasis on the functional importance of intrinsic electrical activity stems from its fundamental incorporation of time as a dimension of neural coding. That is, the efficacy of neurofeedback can only be understood within a model that incorporates time as a facet of information transfer (as that is the basis of the bioelectrical domain), and the reductionist model used in biomedicine does not.

Following is an exploration of neurofeedback training and the model of disregulation, specifically in regards to Parkinson's disease. Interestingly, a neurophysiological probe into Parkinson's disease ends up providing much

evidence and support for the use of neurofeedback as a treatment for the disease, at the same time validating the model of disregulation. Not only does this offer an exciting new prospective therapy for Parkinson's disease, but affirmation of the model of disregulation can influence the way we view the fundamental organization of the nervous system. Accordingly, this research went into the design of a pilot study on the effects of neurofeedback training on Parkinson's disease, specifically parkinsonian tremor and slowness of movement, for which the author has received the support and funding to conduct the following year.

The chapter contents are as follows:

Chapter one contains a historical overview detailing how and why the prevailing model within biomedicine came to be accepted. It primarily focuses on the evolution of the debate between holism and reductionism within neuroscience as sparked by Camillo Golgi and Ramon y Cajal. It traces the outcome of this debate to the emphasis on physiological reductionism that exists in biomedicine today, despite the revelation that the two views do not actually, indeed never did, directly contradict one another.

Chapter 2 is essentially an introduction to basic electrophysiology. A brief discussion of the role of time binding in cortical processes and neurofeedback is given, followed by a short background on the EEG and characteristic brain waves. *Chapter 3* contains a description of neurofeedback training and its process, as well as a discussion of the tenets and implications of

the model of disregulation. Included is how it attempts to account for pathologies both on bioelectrical and neurochemical levels.

Chapter 4 focuses specifically on the pathology of Parkinson's disease. A traditional description of Parkinson's disease is given, focusing on the anatomical and chemical correlates of the disease. Through this, we find that there are considerable difficulties encountered with its diagnosis, and that neurophysiological measures could be helpful. Accordingly, an exploration of the neurophysiological correlates of Parkinson's disease follows, which leads to the work of Rudolfo Llinas, who has done substantial work in studying the interactions between the thalamus and cortex, or what is called thalamocortical dynamics. He has spent substantial amounts of time exploring disorders that he believes to result when there is dysrhythmia in this system, one of them Parkinson's disease. His work includes a detailed mechanism of how parkinsonian tremor and bradykinesia may arise from this dysrhythmia, and supplemented with research done in deep brain stimulation (a widely accepted surgical treatment of parkinsonian symptomology), a possible mechanism of how neurofeedback training might affect Parkinson's disease is crafted.

Chapter 5 brings this research into light with that which is known about the mechanism behind neurofeedback – namely, neuromodulation and long-term potentiation - to arrive at a more complete theory. With this, and information from personal contact with neurofeedback specialists from across the country, a

potential training protocol for Parkinson's disease is developed and a pilot study designed with which to put it into practice, as outlined in *chapter 6*.

Chapter 7 concludes with a brief discussion of the limitations encountered and re-introduces possible implications. It is important to decide whether the mechanism drawn out in previous chapters is complete or if not, if it is sufficient.

Deeper implications will then be touched on, specifically surrounding what affirmation of the model of disregulation could mean for the greater study of the nervous system.

Chapter 1. *Historical Overview*

In order to properly set the context for this discussion, a historical overview is necessary. While history is an essential component of any argument, it is especially important to include it in this one in order to understand how and why the current model of the nervous system that prevails in biomedicine came to be accepted. It allows a conceptual framework in which to place neurofeedback based on its fundamentals, from which its application and the broader implications can be explored.

The overview focuses primarily on the evolution of the debate on what has been considered by many as the two main opposing views in neuroscience: that which emphasizes the function of the brain as a whole versus that which emphasizes the reduction and differentiation of the brain into discrete, functional components (this view will sometimes be referred to as the prevailing model, for the sake of simplicity). A review of this literature – even as simple as the one to be presented here – makes clear that the "one or the other" attitude which grew from the emotive force sparked by the extreme nature of opinions of the two which started the debate – Ramon y Cajal and Camillo Golgi - has perpetuated the exclusiveness of physiological reductionism in the biomedicine when in fact, the two views do not actually present any direct challenges to each other.

A theory of localization of higher functions (i.e. intellect) was embraced from the 4th century through the Renaissance. However, localizing attentions were on the ventricles, not brain matter. It was most often held that the two lateral ventricles served as the common receptacle for sensory information, that the middle ventricle mediated fantasy, ideation, and cognition, and the posterior ventricle was responsible for memory (Finger, 1994). One of the more popular corresponding beliefs reportedly conceived by Galen in the 2nd century B.C. and perpetuated throughout the Renaissance by those including Leonardo da Vinci, was that the ventricles stored animal spirits that mediated action or sensation. Indeed, it was not until the mid 17th century that the Oxford physician Thomas Willis provided impetus for looking at the functional contributions of individual brain parts (Martyn & Allestry, 1965).

This line of thought progressed through the end of the century as increasing numbers of clinical reports suggested that more attention be paid to the brain and its fundamental organization. The 18th century, while presenting many advances in the clinical description of symptoms and diseases, as well as displacing the idea of animal spirits in nerve fluid, did not produce much for the advancement of the said topic. It was not until the 19th century that Julien Jean-Cesar produced what is now widely accepted as the first proof of localization within a brain area, by finding the respiratory center to be located in the medulla. Around the same time, localization within the peripheral nervous system began to be widely accepted (Gibson, 1967). This was largely based on the work of

Charles Bell and Francois Magendie studying the spinal roots of dogs, the former of the two known for suggesting that an entirely new view of the nervous system was needed as, if the spinal roots could be differentiated into sensory and motor areas (as their work demonstrated), the brain may be subject to similar divisions.

This led to research that would often be used to support the extreme approach of cortical localization, where each region of the cerebral cortex was viewed as an independent mental organ dedicated to a distinct, complex mental function. For instance, in their work on the motor cortex, Eduard Hitzig and Gustav Fritsch demonstrated the location in the cortex of a somatotopically-organized region involved in movement (now known as the motor cortex). In their papers, Fritsch and Hitzig maintained that it was worthwhile to search for areas concerned with sensation and intelligence, as they believed it was a possibility that all psychological functions needed centers of the cortex from which to originate(von Bonin, 1960). Some years after this, Sir David Ferrier summarized his work demonstrating the localization of functions in the monkey brain in his book *The Functions of the Brain* (1896), which had a large and lasting effect on the scientific community that embraced it. It was said to be the first spark in encouraging neurosurgeons to turn to functional maps of the brain for guidance. Ferrier remained the leading proponent of cortical localization up through the beginning of the 19th century.

Despite this, it has been reported that those in support of localization remained in the minority prior to, and during much of the 19th century (Finger,

94). However, the debate that inspired this terminology was not born until the later 1800's, arising between the scientists Camillo Golgi and Ramon y Cajal. During this time, little was known about the relationships between nerve fibers, axons, and dendrites (despite developments in microscopy). The major questions centered on the degree to which, if at all, the nervous system formed one large reticular net of fused cells as well as the level of autonomy of each neuronal entity (Gibson, 1967).

By developing a histological technique that stained certain neurons, Camillo Golgi allowed a more precise examination of elements in the nervous system. While his method did not stain all cells, it revealed morphological characteristics of those it did take to, and Golgi claimed in his first papers on this work that it revealed a fused reticulum (a diffuse network of cells within the brain) (Gibson, 1962). This led him to refute the concept of cortical localization and to take a more holistic approach regarding brain function. He would accept the concepts of broad territories, but not precisely demarcated zones as Ferrier and Hitzig proposed. He would later clarify, with evidence from neural development in mind, that the key may be in emphasizing contiguity (close contact) over continuity, a conclusion backed by fellow scientists including August Forel (1887) and Fridtjof Nansen (1887), but his caution of physiological reductionism remained (Golgi, 1906).

With a decided mind from the start, Ramon y Cajal attempted to prove Golgi wrong (Van der Loos, 1967). He set forth by making better and more

distinguishable slides with more intense staining, publishing his findings in a series of papers in which he stressed that he found no evidence whatsoever for the fusion and net formation of either the axons or dendrites of the nerve fibers he saw. He called each neuronal entity absolutely autonomous and went on to study sections from varying parts of the brain, reporting similar findings. Nerve cells, he argued, were independent elements (Ramon y Cajal, 1906). He managed to convince other leading scientists of his findings, many of whom went off to complete influential work on the subject. This included Wilhelm von Waldeyer who, publishing in favor of the Cajal's neuron doctrine, coined the term "neuron." With time, support for the neuronal doctrine continued to increase and heads turned to face the great mystery that grew from its roots; namely, the ways in which supposedly autonomous neuronal elements were able to communicate with one another.

Cue Sir Charles Scott Sherrington, who recognized the gaps between neurons and muscles, and one neuron and another and created the term 'junction synapses' to describe them (Gibson, 1962). Both he and Emil du Bois-Reymond hypothesized that communication between cells could occur either electrically via currents or chemically using excitatory substances released from nerve endings. Years later, Claude Bernard, Paul Ehrlich, and John Langley founded the basis of the study of chemical communication between nerve cells by discovering that drugs interact with specific receptors on cells (Finger, 1994). The discovery of the individual biochemical transmitters began in the early twentieth century, and

continues through today. Indeed, the study of the roles these neurotransmitters play in mediating brain states and behavior has come to dominate the neuroscientific field for reasons traced partly to that discussed below.

A great deal of criticism for the localization of functions to specific anatomical loci arose in the nineteenth century. Golgi, as it was, stood steadfastly next to his position based on his observations of what he called the diffuse nerve network. He was convinced that the literature on recovery of function demanded a holistic orientation. Following opinions took a more moderate approach that claimed that some, but not all functions, could be localized to small parcels of tissue (Golgi, 1906). That is, as Hermann Munk put it (1890), while sensory and motor functions may be confined to these areas, higher cognitive functions might instead be accounted for through the interconnections between such specific sensory areas, which would not appeal to the same anatomical restrictions. Friedrich Goltz (1881) and his assistant and colleague Jacques Loeb (1885) shared these sentiments after conducting many lesion studies on dogs in which they found certain functions to persist after their destruction of the anatomical loci thought to be their point of origin (Rosner, 1974). Thus, although these scientists accepted some form of localization, they rejected physiological reductionism in the strict sense set by Cajal. John Hughlings Jackson, in support of Loeb and Goltz, succinctly pointed out that localization of symptoms and localization of function were not identical; he urged caution when making the theoretical jump

from observable symptoms to precise anatomical locations for the affected functions (Finger, 1994).

To forget that the brain functioned as a whole was a concern and point of emphasis for many in this movement against physiological reductionism. That form quality is something over and above the elements, that the whole is different from the sum of its parts; this was a stance championed by those in the Gestalt movement (for better or for worse), Constatine von Monakow (1911) and Henry Head (1918) during the years of World War I (Finger, 1994). Monakow's work centered on the functional relationships between brain regions, and through it he came to stress that brain lesions can have both proximal and distal effects. That is, he claimed that it is impossible to damage any one part of the brain without affecting other parts. Henry Head then went a step further and claimed that a brain lesion that affects behavior does so by throwing the entire system into disorder, not just by affecting specific parts. He looked upon the damaged brain as a new entity - a whole and novel schema - not simply the old system less one or more discrete parts (1918).

This more holistic way of viewing the brain continues to be equated with what was called the aggregate view of the brain, which held that all regions of the brain participate in every mental function, and that each function is represented diffusely throughout the cortex (Purves, 1997). The original aggregate view of the brain was, in part, the product of Pierre Louren's strong reaction against Franz Gall's strict materialistic view of the brain that came about in the 1820's (Finger,

1994). The viewpoints of Head, Lashley, Monakow and Franz, as touched on above, by no means accord with this extreme. Indeed, their work agrees very well with John Hughlings Jackson (who again emphasized the difference between localization of symptoms and localization of function), who is known as one of the first serious challengers of the aggregate view (Purves, 1997). Perhaps the placement of these scientists as aggregate advocates best exemplifies the problem.

The two schools of thought do not present any direct challenges to each other despite their difference in emphasis. Localization theory was more aimed at answering questions having to do with how the brain is biologically functionally organized, while holism tended to appeal more to those that were interested in understanding why brain-damaged patients might show both positive and negative symptomology, as well as why contextual and situational conditions had an effect on such maladaptive behaviors. Indeed, through time, the former has come to encompass some holistic concerns. Current theory of cortical localization, called cellular connectionism, holds that discrete parts of the mind are responsible for elementary operations, and that more elaborate faculties are made possible by the serial and parallel interconnections of several brain regions (Purves, 1997). Indeed, this sounds very similar the views heralded by Goltz and Loeb over a century ago.

As it is, efforts in cognitive psychology, which is seen as an integrative embodiment of cellular connectionism as it combines the study of structure with the study of function, now revolve around the use of brain imaging technologies

to localize parts of the brain used in complex behaviors, attempting to break these behaviors into simpler mental operations in specific interconnected brain regions. Still, there is great difficulty in demonstrating which compartments of a mental operation are represented by a particular pathway or region of the brain, as well as much obscurity in analyzing mental operations into their component parts. Which is why, when dealing with the complex behaviors head-on - with patients - it was emphasized that even if there is specialization, the brain must function as a whole.

Unfortunately, the localizational and holistic positions were not always seen as noncompetitive which is why, even though one can see elements of both at work in modern day mental health care, there is a decided shift towards the "molecularization" approach to the brain. Some historians have used Lashley's death as a marker for the end of the larger movement against strict cortical specialization within the scientific community (Finger, 1994). It was around this time (late 1950's), that advances in technology took off, and new invasive methodologies (i.e. aforementioned brain imaging technologies, electron microscopy, etc.) allowed examination of the nervous system at smaller and smaller levels. There was suddenly a scientific thrust towards neurotransmitter mechanisms, receptor site properties, and the operation of simple neural circuits that could be monitored in slices in a Petri dish. It appears that the rancor that arose between Golgi and Cajal in presenting the opposing extremes of the debate carried through the centuries, despite the dwindling differences between them, as efforts have always been made to hold one in contradiction with the other.

Developments that were seen to support one were seen with just as equal enthusiasm as opposing the other. Due to this "one or the other" ideology, the physiological reductionism allowed by the boom in technology post-Lashley produced astonishing discoveries that many took as evidence that the key to unlocking the secrets of the mind lay in its fragmentation.

Holism, as it has been expressed in this field, has waxed and waned in popularity and but may be working its way back into the mainstream, at least partly, with the rise of modern cognitive neuroscience. More attention is being paid to the functional roles of the interconnections between the specific anatomical loci that have been elucidated and their importance in information processing. However, the point of focus in which molecularization has strongly presented itself is the greater field of biomedicine, which is the practical application and direct reflection of scientific research. Even though the aforementioned research is happening in branches of neuroscience, the majority of medical research within the field is being done at the molecular level. This may be said to result from, as well as aid in, the compartmentalization of mental disorders: a phenomenon now as easily traced to the role of the pharmaceutical industry as well as it has to the debate so fueled by Ramon von Cajal.

The Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM IV) is the main diagnostic reference of mental health professionals within the U.S., providing diagnostic criteria for the most common mental disorders. It

embodies as well as feeds the mainstream view that disorders are discrete and differentiable. Often it does not incorporate phenomenological distinctions as it reflects the replacement of the psychodynamic models of mental disorders with one centering on their physiological basis in immutable structures (Othmer et al., 1999). It includes information on treatment, and as such is in a symbiotic relationship with psychopharmacology; specificity of drug action has been accompanied by increasing specificity in diagnostic categories.[1] Many who claim that, in reality, disorders cannot be so easily compartmentalized have challenged it. They claim that, as an example, many disorders have unique time courses rather than remain stable over time as the DSM IV portrays (Suffin & Emory, 1995; Othmer et al., 1999).

With the loss of psychodynamic models went the consideration of disorders as functional, and it has been argued that some psychopathologies are better regarded from this perspective (see above challengers). That is, DSM criteria rely on a structural view of psychopathology that looks to some sort of lesion - a hardware problem – as the basis of a disorder, when in reality, many disorders present no evidence of lesion. As far back as the work of John Hughlings Jackson it was found that seizures could arise from healthy brain tissue

[1] Far be it from here to launch an attack on the pharmaceutical industry, but it is not a far stretch to posit that those who stand to profit the most from an increasing number of disorders will do their best to support efforts towards such differentiation. Perhaps that is why pharmaceutical companies, biotechnology and medical device firms financed 57% of funding for biomedical research in the years of 1994 up through 2003 (JAMA. 2005; 294:1333-1342.).

and indeed, disorders such as depression and schizophrenia, among others, are still untraceable to a type of structural deficit (Swingle, 1998). Furthermore, those disorders among many others – including those with a known organic basis (i.e. stroke), respond to therapies that adjust properties at the functional level (such as physical therapy, or neurofeedback), suggesting that a more inclusive model is needed.

Obviously, drugs and DSM IV diagnostic criteria are not without merit; they have shown their efficacy in the support they've given to millions of individuals over the many years they have been in active use. Such criticisms are simply meant to demonstrate the strain generated by the increasing compartmentalization of mental disorders and, as such, act as the premise for introducing an alternative model. A model that, like with the great debate between cortical localization and holistic function, does not present a direct challenge to the prevailing model, but calls instead for a change in emphasis. To change from a bottom-up approach to one that is top-down, positing the physiological level as the regulator of the neurochemical ranks. As such, it presents hope of organizing clinical findings and recent scientific developments that present difficulty when approached by the prevailing, structural model; i.e., that which is best described in the bioelectrical domain, which is the topic of the next chapter.

Chapter 2. The Bioelectrical Domain

It was Richard Caton who, in 1875, was considered the first to record spontaneous electrical activity of the brain, tracking the electrical changes taking place in correspondence to specific peripheral stimuli in rabbits and monkeys (Finger, 1994). Hans Berger, however, is considered the forefather of the field due to his published work in 1929, describing patterns of oscillating electrical activity recorded from the human scalp. He did this using the electroencephalogram, as his technique came to be called, and he believed that analysis of the oscillatory activity could prove useful in measuring and defining biological markers corresponding to human behavior (Cantor, 1999). Indeed it has, and much work has been done since then in analyzing the time structure of recordable wave patterns, establishing close correlations between the frequency spectrum of the oscillations and changes in the central state of the brain.

The development of recording activity from individual neurons, however, brought a decline in interest in field potentials and temporal structures. Findings of the close correlation between location and firing rate of a neuron and its functional properties led to the belief that the message it conveyed was entirely determined by these properties (Othmer, 1999). Single unit studies have given time little attention and as consequence, so has neuroscience in regards to it being a dimension of coding.

However, developments within the rapidly expanding field of research are showing the significance of self-generated temporal codes in cortical processes. For instance, synchronization is believed to have great functional importance in signal transmission and neuroplasticity (Sakurai, 1996). Some even believe that the principle of integration by means of time (time binding) may establish itself as a fundamental aspect of the neural code (von der Malsberg, 1995).

While much evidence remains to be presented before a causal relationship for this can be claimed[2], time binding is thought to provide the theoretical underpinning of neurofeedback (Othmer, 99). That is, the inclusion of time is what differentiates the bioelectrical domain from the neurochemical. It claims that the key organizing principle for the transmittal of information within the central nervous system (CNS) is coincidence in the time domain, defining units of cortical activity that belong together (Singer, 1993). As such, the bioelectrical domain is believed to be the functional basis for the model of disregulation.

The integration we are interested in is that which manifests itself as synchronous, oscillatory activity where differences in the frequency domain act as the defining marker of behavioral states (Abarbanel, 1999). Before we launch into a discussion over how these states can be modified using neurofeedback training, however, a certain amount of background is necessary. Thus, the following consists of a brief introduction into some of the basic properties of the

rhythmic activity within the brain, with emphasis on those relevant to Parkinson's disease.

Fluctuations of field potentials can be recorded with macroelectrodes from the scalp, dura, or from within the brain and indicate that a large number of neurons are engaged in synchronized rhythmic discharges at a respective oscillation frequency. If they were not in oscillation, there would not be recordable macropotentials, as currents associated with synaptic activity and action potentials of individual neurons are too weak (Singer, 1993). These synchronous discharges can occur in a repetitive way, producing oscillatory field potentials (Basar, 1988). Two examples of such activity are the ponto-geniculo-occipital waves that are generated in the brain stem in association with saccadic eye movements and REM-sleep episodes (Jouvet, 1972), and the potentials evoked by sensory stimulation (Basar, 1988).

The EEG is a method of recording this electrical activity at the level of the scalp. It has evolved throughout the last century, from the technology that Hans Berger invented in 1929 for his groundbreaking work on humans, to that as it exists today in a field of computerized neurophysiology: the quantitative EEG (QEEG). The EEG records activity through up to 19 electrodes placed at standardized recording sites on the scalp (**Figure 1**), corresponding to cerebral cortices, usually with two reference electrodes placed on the earlobes. There are

[2] Most likely in the form of behavioral studies, closely examining the relationship between

two basic types of EEG montages used: monopolar and bipolar. Monopolar compares the activity recorded from one electrode to the reference electrode, whereas in bipolar recording both electrodes are positioned to the scalp and are attached to electrically active tissue and the activity between them is compared (Cantor, 1999).

The recordable activity reflects ensembles of generators producing rhythmic activity in several frequency ranges. They generate oscillations that are usually randomly active but, with sensory stimulation, produce what are known as evoked potentials, where the oscillations couple and act together coherently. According to Basar (1988), coherent EEG states are considered internally induced rhythmicities, similar to evoked potentials but without known causal events.

Different states can be identified through observing the spectral compositions of frequencies in the EEG (**Figure 2**):

Delta range (0.5 to 4 Hz) frequency is observed during slow wave sleep and also during pathological states such as anesthesia or coma (Singer, 1993). Delta predominates in children up to the age of 4, but is considered to be strongly pathological if found after that age (Laiblow, 1999).

Theta range frequency (6-7 Hz) is prominent in the limbic structures such as the septum, the hippocampus, and the entorhinal cortex during states of attentive arousal (Singer, 1993). During healthy function it is equated with deep creativity. It is also noted with psychotic states, delusion, and other states

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behavioral states and response synchronization (Singer, 1993)

associated with poor reality testing and with seizure disorders (Peniston & Kulkosky, 1999).

Alpha activity (10 Hz) occurs during drowsiness or states of relaxation and is particularly pronounced over occipital cortical areas (often characterized by creativity and dreamy thoughtfulness). It may be pathologically decreased in mood disorders, chronic pain, and all stress-related disorders (Laiblow, 1999).

Sensory motor rhythm (SMR, also referred to as *Beta I*) is a spindle-like, rhythmic activity in the frequency range of 12-15 HZ that is generated by the recurrent bursting of the ventro-basal nucleus of the thalamus (Thompson & Thompson, 2002). It is detected in the EEG over the central part of the brain across the sensory motor cortex. When this rhythm is present there is attenuation in the conduction of somatosensory information to the cortex and decreased motor excitability, which is why SMR training is used in seizure control (Sterman, 2000). SMR is thus related behaviorally to sustained immobility and an active mind (an external focus of attention, paying attention, sequencing, and information storage and retrieval). It is often depressed in attention deficit disorders, mood disorders, anxiety, panic, obsessive-compulsive disorders, fear, chronic pain, and the entire gamut of stress—related disorders (Laiblow, 1999).

Up to the alpha frequency range, oscillatory activity is of large amplitude and can readily be recorded with macroelectrodes, which indicate that the discharges of a large number of neurons are synchronized and phase-locked to these frequencies (Singer, 1993). This contrasts with the low-amplitude, high

frequency fluctuations in the EEG, which characterize high levels of arousal and attention. During these states, the spectrum of the EEG covers a broad range of frequencies extending from 10-60 Hz. With analysis using refined methods including digital filtering and intracerebral recording with microelectrodes has come additional disclosure of oscillatory activity in the beta and gamma frequencies between 15 to 30 Hz, respectively (Singer, 1993). These high frequency oscillations occur spontaneously both in humans and higher mammals such as cats and monkeys when the subjects are in a state of focused attention (Bouyer et al., 1981; Montaron et al., 1982; Ribary et al., 1991) or when they are performing new and complicated motor acts (Murthy & Fetz, 1992). *Beta II* (16-24 Hz) activity is also associated with states of physiological arousal and response to threat and is elevated in all stress-related disorders, some mood disorders, panic, anxiety, fear, and chronic pain (Laiblow, 1999). Oscillatory components in the *gamma* frequencies (30-60 Hz) range, however, associated with the said sensory and motor processes, are of yet not known to be present in any set pathology.

The probability of occurrence of synchronous activity in a particular frequency range depends on the central states of the brain as well as whether there is the presence of sensory signals and/or the occurrence of motor acts (Singer, 1993).[3] It is commonly held that states of global synchrony at low frequencies up to 7 Hz (delta and theta) are inappropriate for information processing. When they

[3] For a review on how oscillatory activity arises, see Wolf Singer, 1993.

do occur, very large populations of cells discharge in unison, and these self-regulated rhythmic discharges are scarcely influenced by sensory stimuli. As such, these lower wave frequencies (delta and theta) tend to occur during sleep and in coma and anesthesia.[4]

This information is useful when considering findings recounted in the following chapters. Indeed, the information presented can now be considered sufficient as a background with which to discuss mechanics and possibilities of neurofeedback training and the model upon which it relies.

Chapter 3. Neurofeedback Training & the Model of Disregulation

Neurofeedback Training

During the 1960's it was discovered that it was possible to control the amplitude and frequency characteristics of one's own electroencephalogram if provided feedback about those attributes (Glueck, 1975). Many psychologists and medical practitioners, sensing the possibilities such operant control of the nervous system's electrical activity might have for clinical treatment, gave EEG biofeedback its name and began applying it to psychiatric disorders. Within a few years, however, it fell into dispute for reasons that remain unclear. This may be because it became clear that the EEG was, at best, a tool that could be used for confirmation of clinical disorders such as epilepsy and brain trauma. It revealed little about the anatomical/neurophysiologic continuum and human behaviors. In the 1980's, however, the development of computerized EEG diagnostic and feedback instruments brought back a boom in EEG biofeedback use (Cantor, 99). It became feasible to assess and quantify (precisely) an ever greater number of EEG parameters, eventually leading to the development of the system used today.

The therapy, however, has never really recovered from the ambiguous said decline in its popularity that occurred in the 1970's. This is evident in the attention and resources that have been withheld because of its categorization

[4] The functional significance of these low frequency oscillations in natural sleep are thought to relate to processes of memory management and consolidation (Hobson, 1988).

within biomedicine as an alternative therapy. However, an examination of its reported clinical efficacy and the implications the therapy may have on the way in which we view the brain demonstrates that the shortage of interest is anything but deserved.

Neurofeedback, also called EEG biofeedback, is a type of brainwave training. It is a medical discipline that is based in neurophysiology, employing EEG, neuroanatomy, pathophysiology and behavioral medicine (Laiblow, 1999). The therapy, as it exists today, begins with a quantitative electroencephalogram (QEEG) assessment, which consists of anywhere from 2-19 electrodes placed on the head at standardized electrode sites to gather EEG data (**Figure 1**). There exists a tremendous body of research on the abnormal EEG and QEEG patterns associated with various medical and psychiatric disorders as well as a normative database, to which the data collected at assessment is compared (Cantor, 1999). These data then guide the training process. For example, if QEEG findings reveal a disproportionate ratio of theta to beta amplitudes in a given brain region (compared to normal), a conditioning paradigm is set up that attempts to normalize the ratio and stabilize it over time.

During training, there are usually two electrodes placed on the scalp at locations where the EEG activity diverges most from norms, with reference and ground electrodes placed on the earlobes to measure the ongoing brain activity. It is theorized that ordinarily we are unable to influence our brain activity because

we lack feedback on it. However, when we are offered feedback in some form from the portrayal of our brain wave activity on a computer screen a few thousandths of a second after it occurs, it allows us to modify our brain wave patterns through operant conditioning. With the aid of reinforcing stimuli from a therapist modifying the appropriate thresholds, the patient learns to inhibit inappropriate activity and reinforce healthier brain wave activity (as defined by the collective database information), thus inducing enduring changes (Evans, 1999).

Most work in the area has been grounded on research by Sterman and associates who, in the mid 1960's, noticed that an increase in sensorimotor rhythm (SMR) led to a motorically quiet condition in cats (Sterman, 1969). They later established that biofeedback training to increase SMR activity resulted in decreased seizure activity in humans (Wyricka & Sterman, 1968). In the mid 1970's, Joel Lubar and colleagues thought this therapy might be effective for ADHD, as the condition is associated with overactivation of the motor system in addition to deficits in learning. Indeed, subsequent research determined that an EEG protocol that involves an increase in SMR activity (12-15 Hz) while suppressing activity in the theta (4-7 Hz) band significantly improves the ability of ADHD children to focus and concentrate while quieting their hyperactivity (Lubar & Shouse, 1976). Confirmed in a great number of studies, this therapy has become a commonly used and celebrated treatment for both attentional disorders and seizure disorders (Loo & Barkely, 2005; Swingle, 1998).

It has been used for a wide variety of other conditions as well, not limited to: affective disorders (Baehr et al., 1997), schizophrenia and thought disorders (Prichep & John, 1992), dementia (Brenner et al, 1986), closed head injury and neurological conditions (Thatcher et al., 1991; Keller, 2001), stroke (Rozelle & Budzynski, 1995), pain (Pelletier & Pepper, 1977), obsessive-compulsive disorder (Hanmond, 2005), autism (Scolnick, 2005), tinnitus (Mason, 2001) and hypertension (Norris et al., 2001). To date, the emphasis has been on trying to document efficacy of the EEG biofeedback in the context of existing models of psychopathology; namely, renditions of the structural model reinforced by the DSM IV. Because they are well established and self-reinforcing, the appearance of an occasional clinical report that lies outside of the models is unlikely to gain attention, much less compel conviction (Othmer et al., 1999). However, it is argued that existing clinical reports can become mutually supportive if regarded from the standpoint of a new model.

Model of Disregulation

This new model serves as a means to organize both the said clinical findings and recent scientific developments. It has been very well described by Othmer et al. (1999) and Andrew Abarbanel (1999), from which the following material has been adapted, and in reviewing this literature the author found the model of disregulation to rest on two fundamentals. The first is that it relies on

rhythmicity as the main organizing principle in the brain. That is, the model recognizes that most information transfer in the brain occurs via the action potential. However, the nexus between the information encoded in a neural firing event and something we recognize as experience at a conscious level may lie in the collective activity of an ensemble of neurons (Llinas, 1998). In other words, the brain activity we are aware of may be a property of large neuron groups rather than a property of individual neurons. As such, the brain must organize these neuronal ensembles into functional groupings for as long as a particular mental task requires (MacCormac, 1996). This organizing of neuronal activity is conducted either by the brain using rhythmic generator circuits or, alternatively, the outcome of self-organizing cortical-cortical interactions (Hardcastle, 1996).

The self-organizing activity as described by MacCormac and Hardcastle is another way of referring to the spontaneous, intrinsic activity first described by Brown and observed by Berger and others in the EEG. This helps in understanding the model of disregulation's second fundamental: of treating the brain as a self-regulatory control system. With this it views psychopathology in terms of the dysfunction of the brain's neuromodulatory machinery, where the very essence of the problem is disregulation - a malfunction of the brain in its essential regulatory components. That is, failures in the proper governance of rhythmicity can lead to significant dysfunctions. Photic epilepsy, for instance, can be understood in this light. A periodic optical signal (a flashing light, for example) can lead to slight changes in the rhythmic behavior and result in

seizures in vulnerable brains (indicating how sensitive the brain is to the state of its own rhythmicity) (Othmer et al., 1999).

Indeed, many disorders are believed to stem from fundamental instabilities that are perpetuated to an end state of recognizable symptomology (Abarbanel, 1999). It is thought that as the brain successively experiences dysfunction, practice effects will lead to learned misbehavior. Talk therapy and pharmacology (which we will see later on), have the effect of normalizing neurophysiological function and help demonstrate that the normal states are already within one's functional inventory. It is claimed that neurofeedback exerts a similar effect by directly appealing to the mechanisms by which these rhythmic processes are established and maintained. If disregulation is the problem, Othmer writes (99), then a method to regain regulation must constitute a remedy. Neurofeedback attempts to restore the timing mechanisms by operant conditioning in order to act as a regulatory challenge to which the system responded by becoming more capable and stable as a control system.

It has long been the belief that a drug's alleviation of a certain problem weighed in support of that problem having a biological basis. However, the transient effects of drugs (such as stimulants) can be used to argue that the brain is merely changing in its functional state; that the drug simply promotes a shift in the balance of neuromodulatory systems to achieve a different behavioral state. It is then argued that a similar change in state could be accomplished by operant conditioning if the operant is the bioelectrical manifestations of the same

neuromodulator systems (i.e. the EEG). Neurofeedback could then in principle be helpful for almost any mental condition for which medication has been demonstrably helpful. Moreover, it has been shown that by continuing administration of EEG biofeedback, long-term adaptations can result. However, because the brain will have achieved these changes entirely autonomously, there may be no continuing need for drug administration to sustain them.

A central and distinguishing feature of the model is that, as the disregulation is likely associated with certain control regulatory functions, it is not restricted to specific clinical categories. It is not so much in direct conflict with the mainstream view as embodied by the DSM IV, as much as the latter is simply unhelpful if one is attempting to look at neurophysiological generators. That is, the key to the management of these drivers lies in the timing and electrical domain, which is not as accessible to interpretation on a strictly neurochemical level. Surely, the neurochemical domain is capable of explaining how, through neuromodulation, the tone of the nervous system is set at any one time, which then exerts an effect on the timing and therefore the organization of the system. However, a hierarchical system may be more parsimonious with the time domain at the top, in turn impressing its demands on the neurochemical ranks. While it is easy to forget, structural and functional levels are in fact two sides of the same coin, and neurofeedback simply calls for a different organization of the same material that takes the bioelectrical domain into sight. As such, the model of

disregulation may offer insight into the fundamental organization of the nervous system.

The use of neurofeedback training is not necessarily contingent on the acceptance of the model of disregulation, but its discussion is important. While clinical reports act to validate the model, its acceptance by the greater scientific community would support an expansion of the clinical research being done. That is, most of the research within the area has been done within epilepsy and attentional deficit disorders which were treated with an SMR training protocol (as again, Sterman (68) and Lubar (76) found it to led to a motorically quiet condition). Acceptance of the model would mean the acknowledgment of the idea that aberrant rhythmicity in one frequency domain can manifest itself as many different disorders, and can be dealt with accordingly. Surely then, one could more easily make the connection between the SMR protocol and movement disorders, which seem to best fit the protocol's intended purposes. That is, the chief symptomology of Parkinson's disease would seem to match perfectly with a training protocol that has its primary effect in strengthening voluntary muscular control and decreasing involuntary motor fluctuations.

Indeed, specialists from across the country have reported success in achieving exactly this (Seigfried Othmer and Lisa Tataryn, personal contact). Among these scientists, two have published a piece discussing a case study of a patient with dystonia and Parkinson's disease, some of who's symptoms were

greatly alleviated with a few months of training with the SMR protocol (Thompson & Thompson, 2002), but this remains the only piece standing to validate such claims. Interestingly, Parkinson's disease presents a unique case, as it is not clinical reports that lend the most support for its treatment by neurofeedback training, but instead an exploration of the mechanism of neurofeedback through a parkinsonian lens. That is, a look into the neurophysiology of Parkinson's disease ends up unearthing much support for the model of disregulation, which in turn supports efforts for further research within the area.

Chapter 4. Parkinson's Disease & Thalamocortical Dysrhythmia

Parkinson's Disease

Parkinson's disease is a debilitating and progressive neurodegnerative disorder that is known to affect over one million Americans. Without a diagnostic biologic marker, its diagnosis requires frequent clinical reassessment (Jankovic et al., 2000). As it is known today, Parkinson's disease (PD) presents a collection of signs and symptoms known as parkinsonism. Current diagnostic criteria claim that patients can be considered to have PD when they have bradykinesia (slowness of movement) and at least one of the following: rigidity, tremor, or postural instability with no known other cause and do not have any signs considered to be indicative of a type of atypical PD (Koller, 1992; Calne et al., 1992; Hughes et al., 1992). The disease is also associated with other definitive signs, including a lack of facial expressiveness, stooped posture, shuffling gait, micrographia (small, crowded handwriting) and particular impairment in the initiation and sequencing of voluntary movements. Also termed paralysis agitans, or shaking palsy, Parkinson's disease patients often present features in conjunction with their diagnosis that include cognitive disorders (Levin et al., 1992; Starkstein et al., 1992), depression (Melamed, 1997), olfactory dysfunction (Stern et al., 1994), sleep disorders (Kales et al., 1971), and autonomic dysfunction (Goetz et al., 1986).

Pathologically, PD is characterized by severe loss of dopaminergic neurons within the pars compacta of the substantia nigra, a thin band of pigmented neurons within the basal ganglia (**Figure 3)**. It has been hypothesized that cells of the frontal cortex initiate signals for movement, and then send the signals to the basal ganglia, which, through a series of pathways, fine-tune movements in terms of fluidity, speed and reaction time.[5] Other components of the basal ganglia include the globus pallidus, subthalamic nucleus, and striatum; the latter of which can be broken down in the caudate nucleus, the putamen (**Figure 4**), and is where the low level of dopamine is thought to alter the pathway such that the normal response of balance and coordinated movement is not achieved. Involuntary movement (i.e. tremors), on the other hand, is believed to result because the dopaminergic neurons in the basal ganglia no longer fire normally, thus disabling the basal ganglia from inhibiting involuntary movement (more on this below).

It is estimated that approximately 60% to 70% of the dopamine cells within the substantia nigra are lost by the time a patient first presents for clinical evaluation, diagnosis, and treatment. Neuroimaging reveals the loss of dopamine terminals within the striatum to be asymmetric, and to progress over time leading to further clinical deterioration. Histologically, the hallmark of PD is the Lewy body (LB), a cytoplasmic inclusion composed principally of alpha-synuclein. LBs form in the substantia nigra and other select places in the brain, but do not seem to

[5] This conclusion was based on the observation that Parkinson's patients are capable of voluntary

be a rule, as some diagnosed with PD do not develop the inclusions. In addition, although the dopamine loss is the earliest and most marked neurochemical feature of the disease, there are also less marked depletions in the neurotransmitters noradrenaline and acetylcholine, with the possibility of more widespread neuronal degeneration at late stages of the disease (Jankovic, 2000).

The cause of the degeneration of the cells of the substantia nigra has not yet been determined, and thus doctors can only alleviate a patient's symptoms rather than attempt to reverse its course. Research has suggested that Parkinson's may be caused either genetically or through an environmental toxin. Degenerative diseases of the CNS presenting with parkinsonism that should be differentiated from idiopathic PD are progressive supranuculear palsy (PSP), multisystem atrophy (MSA), cortico-basal ganglionic degeneration (CBGD), and secondary causes of parkinsonism. In fact, 25% of patients diagnosed to have idiopathic PD actually have other pathological diagnoses (Hughes et al., 1992).

It has recently been claimed that neurophysiological examinations can be of help in reaching a more accurate differentiation between parkinsonisms on the basis of specific symptoms and signs. Using electrophysiological and anatomical studies in animals, authors have produced a theoretical model of basal ganglia motor circuitry, the dysfunction of which is believed to explain the pathophysiology of some of the symptoms in Parkinson’s disease (Alexander & Crutchjer, 1990). Much of this research is well accepted and has been used to

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movement, but that the movement is characterized by sluggishness and a lack of coordination

support the use of deep brain stimulation (DBS), a promising and widely used treatment for Parkinson's disease. However, the most convincing, encompassing, and complete account of parkinsonian symptomology in terms of physiological dysfunction remains controversial as a result of its broader purpose. That is, Rudolfo Llinas and colleagues give a detailed account of how parkinsonian symptomology may come about as a result of what they call thalamocortical dysrhthmia (TCD); a phenomenon they use as support in postulating thalamocortical interactions as the neuronal basis of consciousness (Llinas, 1998).

Following will be a review of Llinas's work relative to a neurophysiological explanation of Parkinsonian symptomology. Initially one will find an overview of relevant electrophysiological properties of thalamic cells, with which to better understand subsequent information regarding what can result from their interactions. This will then be used as the context in which to discuss how the loss of dopaminergic neurons that characterizes PD can lead to aberrant rhythmicity, and how this dysrhythmia can then give way to parkinsonian tremor and bradykinesia. Such information is used to further understanding of observations and therapeutic effects that can best be explained in similar terms, such as DBS and, ultimately, neurofeedback.

Thalamocortical Rhythmicity: the Work of Rudolfo Llinas

(Koller, 1992)

Electrophysiological properties of thalamic neurons [6]

The study of thalamocortical (TC) neurons essentially began in the 1960's with *in vivo* intracellular recordings (Andersen & Andersson, 1968). Until recently, TC neurons were considered simple relay elements between sensory inputs and the cerebral cortex. However, these neurons are endowed with intrinsic electrophysiological properties beyond a simple relay function (Llinas, 1988; Trimmer & Rhodes, 2004). Indeed, as Llinas puts it, they may be the "fundamental arbiter for global brain states" (Llinas & Steriade, 2006).

There are three types of neurons in the thalamic relay system: the thalamocortical neurons (TCR), the reticular nucleus neurons (RE) that provide inhibitory feedback to control the TCR neurons, and the local interneurons that help coordinate the interactions between the first two (**Figure 5**). The TCR neurons function in two distinct modes: as relay cells that depolarize in response to streams of input, thereby transmitting ascending sensory input, and as oscillatory cells that fire in a collective rhythm, thereby blocking input to the cortex (Abarbanel, 1999). Which modality appears depends on how close the RE and TCR resting membrane potentials are to their firing thresholds. The resting potentials in turn are determined by neuromodulation from brain stem centers. Neuromodulation provides either depolarizing or hyperpolarizing influences to thalamic neurons by adjusting thalamic membrane permeability to ion flow. This

[6] Note: everything within this section not cited otherwise is from Llinas & Steriade, 2006.

process adjusts the firing characteristics of the TCR and RE cells, establishing either the relay or oscillatory state (Abarbanel, 1999).

Thalamic neurons, depolarized from resting potential levels positive to -55 mV, fire tonically both *in vivo* and *in vitro* conditions (**Figure 6**). After hyperpolarization of the cell, a similar depolarizing current pulse produces low threshold spikes (LTS) topped by a large frequency burst of action potentials. At levels negative to -60 mV de-inactivation of a T-type Ca2+ conductance occurs, giving rise, upon depolarization, to reactivation of an inward current through T-type Ca2+ channels (a type of Ca2+ channel). The calcium current can become regenerative and activate Ca2+-dependent spikes, which activate high frequency bursts of Na+ action potentials (**Figure 6**).

Thalamic bursts arise from a hyperpolarized membrane potential level only if the hyperpolarized membrane potential has been sustained long enough to inactivate the T-type Ca 2+ channels and to activate the I_h current (a current carried by Na+ and K+ ions). As such, these two conductances are a prerequisite for the generation of the low threshold spikes responsible for rhythmic spike bursting. The burst response of the thalamic cells is an intrinsic activation mode that can only be evoked by a period of sustained hyperpolarization, and results in well-defined, cyclical patterns in the frequency range of 4-7 Hz. These patterns will be maintained for as long as the cells remain hyperpolarized between bursts.

It is suggested that the sensory motor rhythm (12-15 Hz), alpha rhythm (10 Hz), and theta rhythms (4-7 Hz) appear when inputs from the three systems

are withdrawn from the thalamus (Sterman, 1994). If cognitive processing is withdrawn, alpha appears. If sensorimotor inputs are withdrawn, the SMR appears. And likewise if vigilance is withdrawn, theta appears. It has been found that once novel stimuli generating spike-bursts are detected during low levels of vigilance, then TC cells switch their firing mode from bursting to tonic discharges (Guido and Weyland, 1995). This activity can be continuously regulated by sensory or cortical synaptic input; the latter bring a more powerful source. When these neurons are depolarized positive to -50 mV, they generate subthreshold oscillations at frequencies near 40 Hz (gamma band). This activity is the functional converse of the rhythmicity that supports slow-wave sleep.

Indeed, LTS bursts appear during the hyperpolarized state of TC and RE neurons during slow-wave sleep, but they can also occur on rare occasions during waking. That is, the brain can produce abnormal coherent states that can last for a variable amount of time in which a dysrhythmic state in a portion of the thalamocortical system is stuck in coherent LTS activity while the rest of the system remains in the usual waking state. Llinas holds that such dysrhythmia is generated by membrane hyperpolarization (T-type Ca 2+ deinactivation) in the thalamus and can give rise to a whole gamut of neurological and psychiatric conditions (Llinas et al., 1999; Jeanmond et al., 2002; Spencer et al., 2004).

Thalamocortical dysrhythmia (TCD)

Compared to controls, Llinas and colleagues (1999) found that awake patients with neurogenic pain, tinnitus, Parkinson's disease, and depression all showed increased low frequency theta rhythmicity in conjunction with widespread and marked increase of coherence among high and low frequency oscillation (coherent high frequency activity occurring alongside coherent low frequency activity – more on this below). The coherent theta activity was thought to be the result of a resonant interaction between the thalamus and cortex due to the generation of low-threshold calcium spike bursts by thalamic cells. In other words, due to membrane hyperpolarization, low-threshold voltage gated T-type Ca2+ channels are deinactivated, resulting in spontaneous production of low-threshold spikes crowned by bursts of fast Na+ dependent action potentials with low-frequency rhythmicity (**Figure 6**). Motor cortex neurons project to the striatum such that intrinsic oscillatory activity could propagate in a closed loop extending from striatum to thalamus to cortex and back to striatum (**Figure 5**). This low-frequency oscillation, by activating return corticothalamic pathways, could become entrained through the reticular nucleus and through direct thalamic activation. The result is the promotion of large-scale, low frequency oscillatory coherence.

The excess thalamic hyperpolarization is brought about by either excess inhibition or disfacilitation of the globus pallidus. In Parkinson's disease, dopamine deficiency due to the degeneration of the pars compacta of the substantia nigra has a differential effect of striatal neurons (**Figure 4**). A decrease

in activity of GABAergic projections of the GPi results in increased inhibitory outflow from the latter nucleus. Disinhibition of GABAergic striatal projections to the external globus pallidus (GPe) mediate an increase in excitatory input from the subthalamic nucleus (STN) to the GPi. This consequently leads to the inhibition of GABAergic cells in the GPe that exert an inhibitory effect on the STN. The combined effect of the pathways is a massive increase in inhibitory outflow from the GPi, which constitutes the major subcortical input to the ventral lateral nucleus (VLa), a relay station for motor processing. As a response to repetitive hyperpolarization, VLa neurons show low-threshold rebound excitation at a frequency of 3-6 Hz. This VLa rhythmicity is then relayed to premotor and motor cortices where, at the cortical level, the reduction of lateral inhibition promotes coherent high frequency gamma oscillations in what is called the "edge effect" (Llinas, 2005).

The effect has its roots in the observation that activity in some brain ailments present both theta and gamma frequencies simultaneously. Llinas holds that abnormally persistent co-activation of neighboring thalamocortical regions at different frequencies can result in aberrant high frequency. That is, the low frequency activation of intracortical inhibitory neurons can reduce lateral inhibitory drive and result in high frequency, phase-locked coherent activation of neighboring cortical modules. This is the edge effect; simply a boundary effect seen in the difference in amplitude and facilitation between the responses elicited when high frequencies and low frequencies co-exist.

That this continuous coexistence of a low frequency TC rhythm, disinhibiting neighboring regions and allowing aberrant gamma-band activity in the awake condition, could generate abnormal gamma-band activity was examined through GABA-mediated inhibition with magnetoencephalography (MEG) data analysis. Llinas (2005) writes that, at the cortical level, it seems that GABA-mediated inhibition determines the spread of cortical activation. That is, inhibition modulates the distribution of ongoing thalamocortical rhythms that regulate arousal levels and bind multisensory inputs..

In regards to PD, it has been found that thalamic GABAergic inputs from the basal ganglia play a large role in modulating resonant dynamics during normal rhythm generation and during TCD. The activity of low-threshold spiking inhibitory interneurons is strongly facilitated at frequencies greater than 30 Hz (Gibson, et al., 1999). From this it was inferred that inhibition is central to the generation and maintenance of fast oscillations, and that the spatiotemporal properties of cortical responses are deeply shaped by inhibitory circuits.

Using voltage-sensitive dye imaging at the cortical level, it was demonstrated that high frequency stimulation activated a restricted area near the region of each stimulating electrode, according with information about the patterns of high frequency oscillations during activated states (Contreas & Llinas, 2001). In contrast, as we know, during low frequency brain rhythms long-range cortical coherence is shown. Indeed, one study applied a GABA-receptor block

on the focus area and found that activation elicited by the 40 Hz stimulation spread laterally over most of the available cortex (Llinas, 2005).

To sum so far: in Parkinson's disease, the excess inhibition produced by hyper active pallidal input into the motor thalamus produces hyperpolarization of thalamic relay cells, with the consecutive deinactivation of T-channels and the appearance of low-threshold calcium spiking and low-frequency oscillation. This oscillation then produces the edge effect by decreasing lateral inhibition; a phenomenon that can be seen by examining the inhibitory role of GABAergic interneurons at the cortical and thalamic level. Maintaining this activity would recruit cortical feedback firing and an abnormal, low frequency coherence would form, leading to the existence of a large invariant oscillatory state. The resultant disconnection of the thalamus by moving it into the slow-oscillatory regime would remain there until the membrane is moved to a less negative potential.

A general condition of TCD is the presence of both positive and negative symptoms. It was recognized as far back as John Hughlings Jackson that patients with many characteristic neurological disorders appeared to present both positive and negative symptoms (Finger, 1994). That is, deaf patients cannot hear but may have loud buzzing in their ears, Parkinson's patients are paralyzed but show tremor. Llinas (05) holds that positive symptoms (i.e. tremor) are generated by aberrant gamma band activity seen that is activated internally, out of context (as

seen in the edge effect). The localization of the low frequency oscillations, on the other hand, is thought to determine the negative symptoms (bradykinesia and rigidity). With this, it is held that particular symptoms correspond with dysrhythmia of a particular cortical region. Tremor could result from the dysfunction within the lateral motor and premotor cortex, while the anterior supplementary motor area is proposed to be dysrhythmic in bradykinesia. The same holds for other disorders arising from dysrhythmia. Neurogenic pain, for instance, may reflect aberrant activation of the insular and other nociceptive cortices (**Figure 7**).

Branching Out With Bradykinesia

The information presented thus far serves as a framework with which to place related findings, simultaneously clarifying these pronouncements and enriching Llinas's argument while doing so. For example, the presence of low frequency oscillatory activity has long been acknowledged to be associated with parkinsonian tremor, as well as its disappearance when the patient is engaged in voluntary movement (Shanhini & Young, 1976). People have observed that in advanced stages parkinsonian tremor influences the inception of voluntary action, as its frequency is capable of attracting other repetitive movements (Carboncini et al., 2001). It has also been found that in most instances, Parkinsonian patients initiate contractions during the descending phase of the oscillation, and produce

the agonist burst after the mid part of the tremor cycle (Wiezbicka et al., 1993). That is, patients with PD tend to time the onset of agonist muscle activity at the elbow or wrist with the time of activation of the same muscle in any ongoing tremor (Hallett et al., 1977).

In doing so, tremor can be a factor in prolonging action times, slowing the initiation of movement. As such, it may contribute to bradykinesia. Indeed, in one of his earlier works, Llinas found what he believed to be support for this pathophysiological link between tremor and slowness of movement in PD in the coupling of voluntary movement within the thalamic cortical motor loop. He showed, using magnetoencephalography (MEG) that the 3-6 Hz tremor in PD was accompanied by rhythmic activity at the diencephalic level as well as in the lateral premotor, somatosensory and somatomotor cortices, and that the individual peak in tremor frequency represented a high-end cut off point for the normal frequency. Thus, as he phrased it, the slowing of repetitive movements in PD may result not from rigidity but from a reduced clocks rate (in the 3-6 Hz tremor range) of a central timekeeper.

This may help in understanding how seemingly unrelated therapies can achieve similar alleviation of parkinsonian symptoms. By increasing excitatory synaptic drive, a PD patient can potentially break out of the coherent vortex that the edge-effect produces. It has been claimed that this excitatory increase is how both surgical micro-lesions, by removing the tonic inhibitory input to the

thalamus, and music therapy (when PD patients hear a marching tune, for instance, they find they have greater voluntary motor control) have their effect. It is also how deep brain stimulation (DBS), one of the more celebrated therapies for Parkinson's disease, exerts its effect.

Deep Brain Stimulation

The association of tremor with low frequency oscillations within thalamic regions has come into a broader spotlight largely because of the success deep brain stimulation has experienced in treating Parkinson's disease (Jeanmonod et al., 1996; Schnitzler & Gross, 2005; Elble, 1996). Deep brain stimulation (DBS) is a surgical procedure that has been used to treat a variety of neurological symptoms, most commonly those associated with Parkinson's disease such as tremor, rigidity and bradykinesia. DBS consists of the surgical implantation of a neurostimulator with which to deliver electrical stimulation within specific areas controlling movement, usually the subthalamic nucleus (STN) or the pars compacta of the globus pallidus (**Figure 8**).

A great deal of literature on the possible mechanisms by which DBS works has been written by the neurosurgeon Andres M. Lozano. Lozano found, recording from a single thalamic neuron in a specific nucleus of a patient with a parkinsonian tremor, that it fires in bursts in synchrony with the tremor at 4-6 Hz. This is to be contrasted with what is categorized as normal behavior where the

thalamic neurons fire randomly, Lozano writes. "When the random pattern changes to a synchronous pattern the tremor appears" (Lozano, 2001). Thus, he believes the treatment strategy is to go into the thalamus and stop it from behaving in this way.

Although the precise mechanism of action is not clear, it has been surmised that DBS produces a functional block of the target. The many mechanisms currently held as possibilities all differ in respect to how this functional block is achieved (depolarizing block, jamming, energy depletion, synaptic failure, channel blocking, anterograde propagation, retrograde propagation, activating inhibitory mechanisms, non-neural cells, all or some or none of the previous). But in regards to a general mechanism, that which is accepted as the physiological source of tremor sounds very familiar. That is, most literature on DBS will trace the lack of dopamine found in parkinsonian brains to hyperactivity of the GPi. Which again, is seen to be due to removal of inhibition coming through the striatum and increased excitatory drive from the STN. The resultant inhibitory outflow is then traced from the GPi to the thalamus, cortex, and brainstem locomotive areas.

As such, theories tend to center around the inhibitory role of DBS on its target neurons, for which there exists much evidence. At the outset, clinical effects of DBS seem to mimic lesions in the same target. Positron emission tomography (PET) studies of pallidotomies and DBS at the GPi suggest that both procedures activate the same motor areas. Activation of these motor areas is

thought to result from removal of excessive inhibitory outflow from the globus pallidus to thalamus and cortex (Cebbalos-Baumann et al., 94). In animal models of PD, it has been found that neuronal activity is increased in the STN and GPi, and that lesions of these structures result in improvement (Obeso et al., 2001). Indeed, high frequency DBS of specific brain targets simulates the effect of a lesion without damaging brain areas.

Some have found stimulation of the STN at frequencies at 75 Hz to 185 Hz to suppress spontaneous activity in the nucleus and generate new patterns of recurrent bursts of spikes. One mechanistic conjecture for why this may occur is that there is a depolarization blockage followed by release of local inhibitory neurotransmitters (Lozano, 2001). This may lead to subsequent jamming of abnormal firing patterns. Indeed, some consider the best evidence in DBS to be that it may be working by activating inhibitory mechanisms by enlisting GABAergic nerve transmission. That is, it is currently theorized that deep brain stimulation may exert its effect by releasing GABA through stimulation of GP, activating axonal terminals from the striatum or external segment of the Gpe (Lozano, 1995). One study explored this through the application of muscinol, a GABA agonist to STN of PD patients and found it to produce therapeutic relief of tremor, bradykinesia and rigidity similar to those achieved with DBS (Levy et al., 2001; Pahapill et al., 1999). Llinas would probably speculate that this improvement occurred because of an increase in the GABA-mediated lateral

inhibition, the lack of which he believed was responsible for the parkinsonian symptom-inducing edge effect.

While the success of the DBS supports Llinas's work, much remains to be answered. For instance, and very interestingly, within the DBS population there are patients whose tremor disappears altogether after stimulating for 24 hours a day for one to two years (Lozano, 2001). This striking example of neuroplasticity induced by DBS has been left relatively unexplored. It seems that much of the lack in understanding of the mechanism by which DBS works stems from the fact that the electrode is affecting an unknown number and unknown kinds of neural elements to an unknown distance, and that electrical stimulation has effects in both anterograde and retrograde directions. It is uncertain how much of the stimulation could be causing neural plasticity and how much it is acting neuroprotectively (Loranzo, 2004).

The same questions could be asked of neurofeedback. Loranzo, at the end of an editorial (01), proposed the possibility of using DBS as a means of modulation for other purposes, such as treating psychiatric disorders or cognitive enhancement. It is fairly clear that neither he nor Llinas were familiar with neurofeedback training when in fact, it is a very real possibility that target and the mechanism of modification of DBS and neurofeedback is the same. Indeed, an exploration of the neurophysiology of neurofeedback may be helpful in

elucidating certain unanswered aspects of related fields - such as the phenomenon of neuroplasticity in DBS.

Chapter 5. Neurophysiology of Neurofeedback

Indeed, if neurofeedback is to make effective and long-lasting changes in neural circuitry, those circuits must be adjustable by feedback control as well as be able to maintain those adjustments over time. The systems involved must be plastic. Thus, neurofeedback is thought to make these changes through the two mechanisms subserving plasticity: neuromodulation and long-term potentiation (Abarbanel, 1999).

Neuromodulation is a process by which the electrical properties of a neuron change as a result of synaptic stimulation, but is to be contrasted with the faster-acting neurotransmission. In one mechanism of neuromodulation, the flow of Ca+ into cells can change membrane potentials as well as precipitate intracellular chemical and structural changes so that the firing characteristics of the postsynaptic neurons are modified.

This process is best understood in the ascending modulator control from the brain stem. There are four major brain stem systems; the locus coeruleus (noradrenergic), the nucleus basalis and surrounding areas (cholinergic), the raphe nuclei (serotonergic) and the central tegmental area and substantia nigra (dopaminergic). These centers respond to incoming stimuli and discharge to higher centers (Derryberry & Tucker, 1990). For instance, the noradernergic system mediates the “fight or flight” response by responding to a range of cues

which arouse fear and then facilitate activity in higher centers during stressful encounters, producing a number of useful prepackaged motoric responses.

Neuromodulation seems to be a central mechanism in subserving neurofeedback in multiple ways. First off, ascending brain stem modulation of thalamic and limbic centers act as switches between states, rates of group oscillations, and other changes in circuitry. At the same time, limbic centers exert neuromodulatory control over several centers enabling the same neural network with more than one type of neuromodulator to carry out two entirely different functions (Derryberry & Tucker, 1990; Isaacson, 1980). The human sleep regulating system is also an example of this, as different neuromodulatory input maintains the cortex at different levels of consciousness. Because neuromodulation functions by a system of nonlinear dynamics, small changes in neuromodulation can cause significant changes over time in the functioning of the system modulated. Thus, only a few sessions of neurofeedback can lead to major behavioral effects (Elbert et al, 1994).

Long-term potentiation (LTP) has been studied extensively in the laboratory for over three decades and is widely thought of as a neural basis for learning and memory (Lynch, 1990). It is the process by which neurons respond to repetitive afferent signals by increasing the efficacy of their receptors in a way that persists after the trains of stimuli cease. Some of the component processes suggested for LTP include changes in the arrangement of synapses, the size of

synapses, their number, and synapse formation and elimination (Wolff et al., 95). There is a continuous turnover of synapses throughout life, and this includes changes in the number of synaptic junctions per axon terminal, and the branching patterns of dendrites and terminal axons. These changes occur on the order of days to weeks, and are presumably programmed into neuronal circuitry during slow-wave sleep mediated by the theta rhythm (Karni et al., 1994; Winson, J., 1992). This process of resonance is the facilitation of information exchange between brain centers resonating at the same frequency, and is thought to be the physiological function mediated by group oscillations relevant to neurofeedback (Lopes da Silva, 1991).

A relationship has been established between LTP and high frequency stimulation. Many researchers have found, for instance, that electrical stimulation of the mid brain reticular formation enhances and facilitates behavioral conditioning (Thompson, 83; Weisz et al., 1984; Bergis et al., 1990). However, LTP has been found to occur throughout the brain, such as within motor cortex. Interestingly, in this case it was also found that for LTP to occur afferent stimulation from both the ventrolateral thalamus and sensory cortex was required (Iriki et al., 1989).[7]

In order to see how all this comes together, take, as an example, a child with ADHD attempting to moderate his/her theta-SMR ratio. During the training

process, the child receives visual information (say a balloon) corresponding to the portrayal of her EEG on a computer screen monitored by the specialist. If SMR is increased, and theta depressed, the child will receive reinforcing stimuli in the form of upward movement of the balloon. The prefrontal cortex monitors the level of the balloon through afferents from the visual cortex and signals the septal-hippocampal system. There are certain pathways (from the brain stem, thalamus and hippocampus back to the PFC, from the brain stem and thalamus to the hippocampus, and so on) available to neuromodulate the prefrontal activity. Directly, through the hippocampus, the brain stem or the cortex (or perhaps all three), it can regulate the frequency distribution of the thalamus and other sites to produce a decreasing theta-SMR ratio. Rehearsal of these activities during ongoing neurofeedback sessions can then stabilize the system through LTP.

The only published work on the use of neurofeedback training with Parkinson's disease was presented by Thompson & Thompson in 2002 in which they presented a theoretical framework for using a combination of EEG biofeedback and regular biofeedback with clients who have movement disorders. This framework was demonstrated through the presentation of a case study - a woman with a dual diagnosis of PD and dysonia [8]– and her reaction to a treatment

[7] It has been noted, however, that in these processes, LTP does not occur in the thalamus itself as this leads to stability that preserves the thalamus stability as an unchanging relay and gating station (Lee & Ebner, 92).

[8] Dystonia, a condition characterized by variations in muscle tone ranging from hypertonic at times to repetitive, involuntary and usually twisting movements, is an incredibly disabling illness that is often a side effect of L-dopa treatment. Because of the similar symtpomology and believed

with the said regiment. They proposed to attempt to increase the production of 12-15 Hz activity (SMR) at the same time as train the autonomic system for a calm, relaxed state (RSA training). This was thought to be associated with decreased firing of the red nucleus, which in turn as links to muscle spindles that have innervations in systems which have been shown to be receptive to operant conditioning [9]. This then, was thought to result in a decrease in undesireable muscle movement and tone that characterizes movement disorders [10].

Thus, it was hypothesized that training for increased SMR activity correlates with a decrease in muscle tone and perhaps a more balanced gamma motor neuron involvement in muscle tension that may translate into a reduction of abnormal and unplanned movements. That is, if one critical factor in dystonia is a

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anatomical roots that it shares with both PD and Tourettes syndrome, with the latter having been shown to be receptive to NF treatment, it was thought that dystonia and PD might then also be receptive to a similar NF paradigm.

[9] Research as demonstrated that NF can affect muscle spindle activity (Sterman, 2000). The muscle spindle is a stretch receptor that monitors the length of skeletal muscle and can be affected by both autonomic and SMR activity. It is composed of intrafusal muscle fibers that lie within the spindle, parallel to extrafusal fibers, and are innervated by gamma motor efferent fibers from the ventral horn of the spinal cord, which maintain the sensitivity of the spindle. The contractions of the large muscle fibers are facilitated, smoothed, and refined by the action of the gamma motor efferent pathways to the intrafusal fibers of the spindle. Short latency paired contraction and long-latency smoother (afferent responses) contraction are governed by this spindle activity (Marieb, 1998), and it is the long latency fibers that SMR is thought to affect. The intrafusal fibers of the muscle spindle receive input from connections to the red nucleus in the mid brain and send sensory information back to pathways that eventually influence red nucleus activity (Sterman, 2000).

[10] Studies conducted by Sterman et al. (2000) found a suppression in neck muscle activity and a jaw closing reflex with the emergence of SMR activity that implicated the gamma motor neuron pathway and muscle spindle system as being uniquely involved and related to alterations in SMR activity. The shift in motor excitability that has been observed during SMR activity is thought to involve reduced output from pathways concerned with the execution and coordination of voluntary movement. Also, there is a reduction in motor pathway cellular and reflex excitability and in muscle tone during SMR activity (Sterman, 2000).

problem in the processing of muscle spindle input (Hallett et al., 1999), then encouraging a mental state which correlates with decreased motor excitability and decreased muscle tone should have a positive effect on dystonia. Increases in SMR, Thompson writes, do correlate with this (2002). It appears that SMR is merely a flag that signals this mental state. Using this flag then, should enable one to train a patient using operant conditioning to sustain the desired state wherein muscle tone is decreased in association with changes in the gamma motor neuron muscle spindle system.[11]

Mary, who exhibited the characteristic Parkinsonian low SMR and an unusually high alpha peak (eyes open) at 9-10 Hz, went through 42 one-hour treatment sessions over the course of 18 months. In addition to the RSA training and SMR conditioning, one inhibit was placed on slow wave activity (6-10 Hz) and another on high beta activity (25-32 Hz). Overall, training was associated with significant reduction in dystonic movements. Additionally, the client became able to use diaphragmatic breathing to cue herself to turn on a mental state associated with increased SMR production and thus control incidents of freezing. It was found that over many months with intermittent or no sessions, the improved quality of life was maintained.

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[11] In addition, the autonomic nervous system can also affect muscle spindles through the direct sympathetic connections to muscle spindles, and the large sympathetic output from the posterior hypothalamus to the tegmentum of the midbrain, which includes the red nucleus.

Thus, neurofeedback involves the patient consolidating an enhanced capacity to regulate state changes and gatings of signals between parts of the brain such that capability is improved (Abarbanel, 1999). This process yields long-lasting results compared to stimulant medication treatment of certain disorders – say ADHD - because it employs the same sort of neuromodulatory control and LTP that practice does in stabilizing such sensorimotor skills as riding a bicycle. Which factor, the brain's capacity to self-regulate, or the particular states into which it regulates itself, or better, what combination of these factors contribute to neurofeedback's therapeutic effects, remains unclear (Abarbanel, 99).

In regards to Parkinson's disease, let's review what we've learned. Given the success epilepsy and ADHD have had training to increase SMR and inhibit theta, it was hypothesized it would also have an effect in movement disorders, specifically PD. Specialists from across the country confirmed this, but there has only been one published case study on neurofeedback training in Parkinson's disease, which we just reviewed. With it we learned of a possible mechanism behind SMR training. From Llinas, however, we learned that Parkinsons's disease patients characteristically exhibit excess theta activity, and of the physiological pathways through which this abnormality can lead to parkinsonian tremor and bradykinesia. This, we then saw, accorded with the hypothesized mechanism behind DBS. Through neuromodulation and long-term potentiation then, it is hypothesized that neurofeedback training could treat

parkinsonian tremor and bradykinesia by decreasing theta activity and increasing SMR over the appropriate cortical loci.

Using this information, the author put together a possible training protocol for PD, which will be using it in a pilot study to be conducted later in the year through the support of a grant from Struthers Parkinson's Center. In conjunction with a neurofeedback specialist, as the following design details, the study will examine the effects of protocol training for an increase in SMR activity and a decrease in theta on tremor and bradykinesia as well as attempt to create a profile of PD using the QEEG information collected from the participants. In its entirety, the study is expected to begin in July of this year and last approximately 5-6 months.

Chapter 6: Neurofeedback Training for Parkinsonian Tremor and Bradykinesia: a Pilot Study.

Study Design

Subjects are expected to consist of 10-20 persons diagnosed with idiopathic Parkinson's disease, recruited from the patient population of Struthers Parkinson's Center in Golden Valley, MN. They will be divided into two subject groups matched with best efforts in age and PD profile. One group will receive neurofeedback treatment and the other will not.

The main interest is in examining differences in symptomology between the two groups as the study progresses, but within group, individual QEEG information will also be collected. Again, the hypothesis is that an increase in SMR activity and/or decrease in slow-wave theta will lead to a decrease in tremor and bradykinesia. However, as the overlaying objective is achievement of clinical benefit, room exists for variations in the protocol to occur, which, when analyzed in conjunction with the QEEG information, may produce equally valuable data.

Procedure:

The study consists of three phases:

I. Initially, all subjects will undergo preliminary quantitative

electroencephalogram (QEEG) assessments by an evaluator blind to the subject's condition. The assessment will consist of the quantification of a number of different characteristics of the electrical signals, including the amplitude, frequency distribution, locus and symmetry. By using a normative EEG database with which to compare this information, the neurofeedback specialist can develop a guide for training strategies. This data will serve as the baseline, thus enabling each patient to act as his/her own control.

II. Within a few weeks of the preliminary analysis the subject will begin the treatment phase. With the guide of a certified neurofeedback specialist, the treatments will occur twice a week for 12-15 weeks, for a total of 24-30 sessions. Every three to five weeks, beginning with an initial clinical assessment, study subjects in both groups will undergo a clinical assessment with a movement disorder specialist.

III. After the cessation of the treatment phase and completion of the fourth and final clinical assessment, the subject will undergo a post-assessment QEEG evaluation.

Training Protocol

While a highly individualized therapy, with each protocol tailored to meet the characteristics of the QEEG assessment, this variance will mainly take the

form of small deviations in training frequency and electrode placement. Success has been reported with single-channel electrode placements at C3-C4, F3-F4, Fp1-Fp2 and P3-P4 (**See Figures 2 & 3**), or two channel trainings at C3-T3 or C4-T4, training on the differences of the two channels, and inhibiting on their sum (Siegfreid Othmer, 2005). Specialists reported success in training an increase in SMR activity while decreasing slow-wave theta and high-frequency beta (for motor fluctuations and rumination).

The present study will initially use two-channel difference training at C3 + C4 with standard inhibits for high frequency activity (20-40 Hz.) and for slow activity in the 4-7 Hz range. The reward frequency will start at 12-15 Hz (SMR) for all subjects and be adjusted as indicated by client responses. Responses include information from additional channels collecting electromyography (EMG), temperature, and galvanic skin response (GSR) information.

Clinical Assessment

Each study subject will undergo a clinical assessment at Struthers Parkinson's Center every three to five weeks with a movement disorder specialist. The assessment will consist of the physician's completion of the Unified Parkinson Disease Rating Scale and the subject's completion of the Schwab and England Activities of Daily Living (**see appendix**).

Neurofeedback specialist

John S. Anderson is the founder and director of the Minnesota Neurotherapy Institute in St. Louis Park, MN. He is certified in biofeedback and neurofeedback by the Biofeedback Certification Institute of America (BCIA) and has worked in the field since 1974, now teaching and consulting for neurotherapy programs in addition to holding his private practice. He has experience in treating a menagerie of clientele with disorders including ADHD and other learning problems, chronic pain, addiction disorders, post-traumatic stress disorder, and performance enhancement, among others.

Technology

QEEGs will be collected using a Deymed 32 channel EEG device (www.deymed.com) with NeuroGuide software. The training will be conducted using the NeXus-10, a wireless biofeedback system with ten channels for data acquisition, four fast EXG channels for electrophysiological signals such as ECG, EMG, EEG, EOG and SCP, with 6 AUX channels for respiration, Skin conductance (GSR), Oximetry, High resolution temperature, or BVP (photoplethysmography). It is used in conjunction with BioTrace+ Software. (http://www.mindmedia.nl/eng/index.htm).

Chapter 7. Conclusion

Thus, we have carved out a neurophysiological mechanism by which neurofeedback training might act in Parkinson's disease, providing support for further research into its use as a prospective therapy for the disease. While it provided enough support to receive funding to conduct a pilot study, it will be the outcome of the study that determines the implications. If the study produces positive results, in that the patients undergoing training experience a decrease in tremor and bradykinesia due to a decrease in excess theta activity and/or an increase in SMR, not only would it serve in validating the treatment strategy as a therapy for PD, but also lend support in affirming the model of disregulation.

It may be that there won't be any significant differences between subjects and controls after training. Gearing each training protocol to the individual will minimize the chance of this, so that the most likely failure in the hypothesis would occur if the subjects require a training protocol that doesn't involve an increase in SMR and/or a decrease in theta. If, however, even with a completely different protocol there were still no difference, the possibility of therapy having no effect then becomes real. Whatever the outcome, the QEEG will be very

useful in collecting information on the neurophysiological profile of PD with the initial baseline reading as well as whatever changes occur thereafter.

This information is also hoped to curb the problem of not including an active control group, which would receive a type of mock-feedback training rather than simply receiving none at all. The possibility of having such a group was discussed at length but decided against after consulting neurofeedback specialists. Apparently the subject can tell fairly quickly that they are not receiving accurate feedback. How they would be able to perceive this immediately, however, seems to conflict with the almost complete lack of phenomenal awareness that is characteristic of neurofeedback training.

That is, while phenomenal awareness does accompany resultant behavioral changes, it is reported that most people are phenomenologically unaware of the process by which these changes come about. Many people, in describing the experiential aspects of the therapy, claim that achievement of the target state is incommunicable (John Anderson, personal contact). Often there is no immediate phenomenological feedback. "It's like the brain is teaching itself," is a common report. That conscious experience is not necessary for successful conditioning may help explain the achievement of similar results using neurofeedback with comatose patients (Cantor, 1999). And it also supports the use of mock-feedback in an active control group. This idea may be more useful to future studies than the one at hand, however, as whether such a group will be

included in the present study will most likely be a decision based on financial considerations.

Again, the argument thus far has been that if neurofeedback training results in a decrease in tremor and bradykinesia due to the modification of the appropriate rhythmicities, the model of disregulation will be supported. While neurofeedback training can be used without prescribing to the model of disregulation, an affirmation of the model the therapy is based on could mean several things. First, remember that the model of disregulation has two central tenets, the first being its reliance on rhythmicity as the main organizing principle in the brain. The model holds that the nexus between the information encoded in a neural firing event and something we recognize as experience at a conscious level may lie in the collective activity of an ensemble of neurons (Llinas, 1998). As such, the brain must organize these neuronal ensembles into functional groupings for as long as a particular mental task requires (MacCormac, 1996). This functional grouping is marked by coherence (constant phase difference over time), and as we saw in thalamocortical dysrhythmia, coherence can also be indicative of pathological states. The second fundamental of the model of disregulation then, is that it treats of the brain as a self-regulatory control system, so that psychopathology is viewed in terms of a malfunction of the brain in its essential regulatory components. Thus, the widespread coherence is believed to be caused by failures in the proper governance of rhythmicity, which can then lead to significant dysfunctions.

An acceptance of the model of disregulation would mean the recognition of these tenets by the greater scientific community, and not only would that go to support an expansion of the clinical research being done, but it may do so by affecting deep-seated, foundational ways of viewing the nervous system. Again, the model of disregulation is not so much in direct conflict with the mainstream view as embodied by the DSM IV, as much as the latter is simply unhelpful if one is attempting to look at neurophysiological generators. That is, the key to the management of these drivers lies in the timing and electrical domain, which is not as accessible to interpretation on a strictly neurochemical level. While the neurochemical domain is capable of explaining how the tone of the nervous system is set at any one time, which then exerts an effect on the timing and therefore the organization of the system, a hierarchical system may be more parsimonious with the time domain at the top, in turn impressing its demands on the neurochemical ranks. While it is easy to forget, structural and functional levels are in fact two sides of the same coin, and neurofeedback simply calls for a different organization of the same material that takes the bioelectrical domain into sight. As such, the model of disregulation may offer insight into the fundamental organization of the nervous system.

The inclusion of time as a mediator of coherence was one of the main issues that separated the model of disregulation from the structuralist model of biomedicine. Thus, the case can be made that validation of neurofeedback is affirmation for the model of disregulation, which in turn supports a view of the

nervous system in which time is an influential dimension of neural coding. While a discussion of time binding is outside of the scope of this paper, it is important to consider the implications of a model that includes the bioelectrical domain.

In this case, was the top-down method of explanation sufficient ? We moved from the level of global brain waves to specific frequency domains, traced their effects through the thalamocortical system and ended at the loss of striatal dopaminergic neurons. However, the question remains as to whether we would have been able to come up with this explanation starting with electrophysiological properties if we had not already had information on the neurochemical characteristics of Parkinson's disease. While the emphasis should not be the directionality of the explanation, but instead the inclusion of all domains, it does remain more parsimonious and effective to explain from the bioelectrical down to the neurochemical. However, acceptance of the model of disregulation would make it so that this method of description is not just economical, but essential. Not only in describing pathologies as the result of disregulations in rhythmic governance, but in order to adequately account for cognitive events, which are characterized by more complex forms of coherence. For, while it is possible to break the whole into parts, and indeed it is often necessary, the temporal properties resulting from large assemblies of neurons are something over and above the sum of all individual signatures and their neurochemical baths. Undeniably, this is an elemental property of consciousness.

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APPENDIX

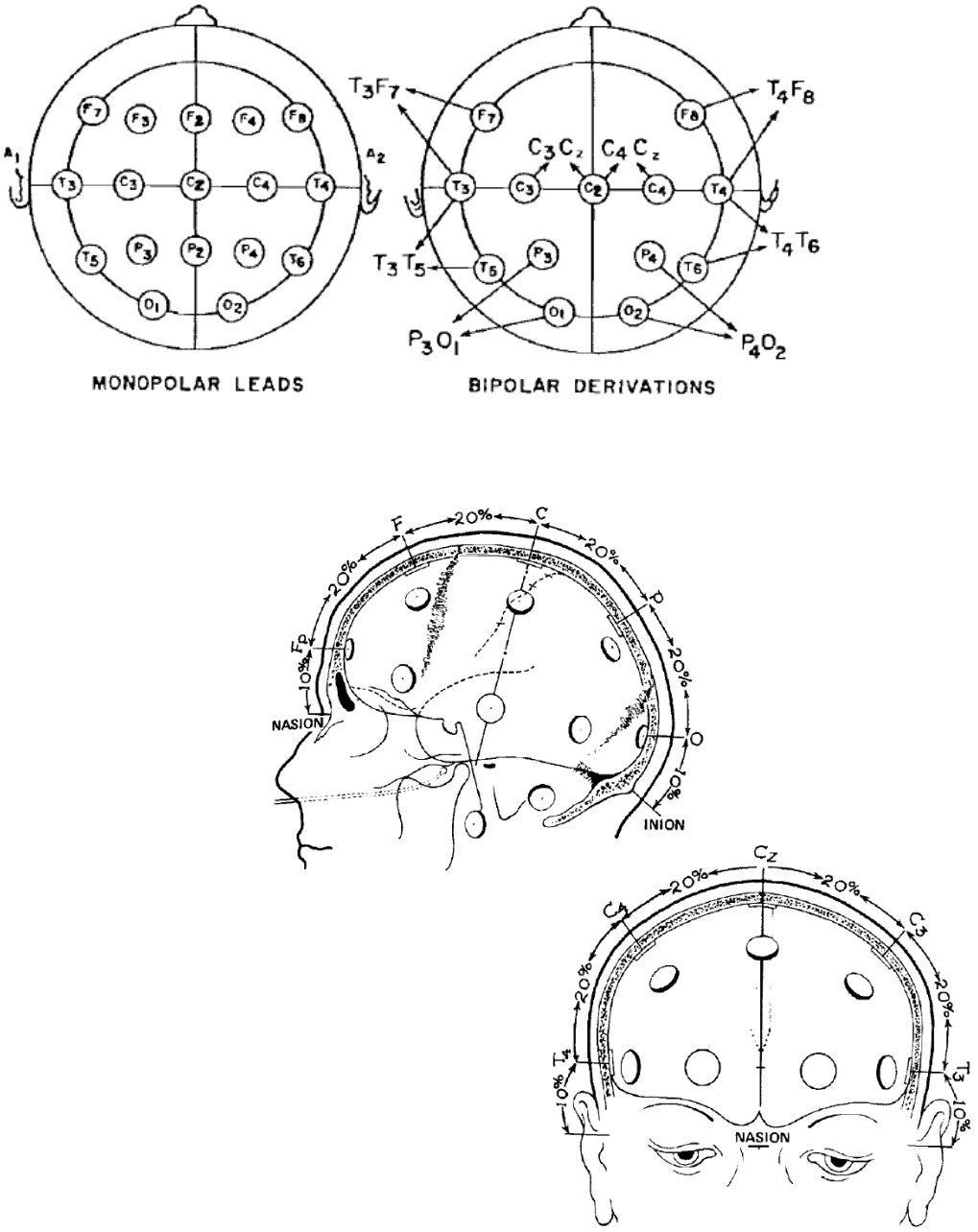


Figure 1. Electrode placement in the 10-20 electrode system. (Fp = frontal pole; C = central; P = parietal; O = occipital). Top: the left head diagram shows the monopolar electrode sites, and the right head diagram shows the monopolar pairs used for bipolar derivations. Bottom: electrode spacing at 20 % intervals (adapted from Cantor, 1999).

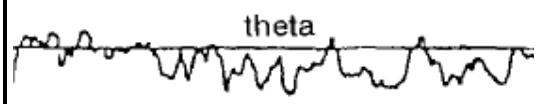
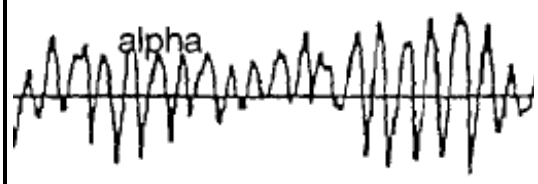
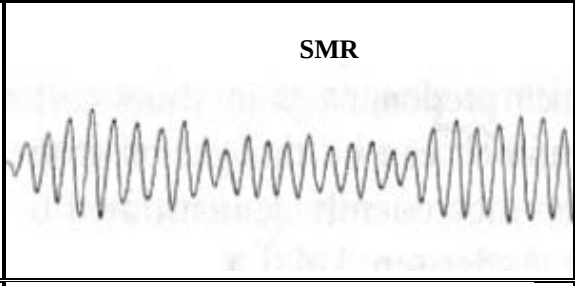
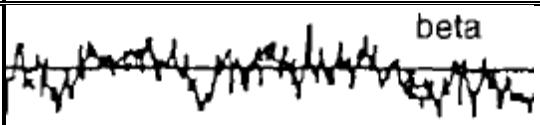
THETA: 4-7 HZ **SLEEP AND MOMENTS OF DEEP CREATIVITY.** **PSYCHOTIC STATES, DELUSION, SEIZURE DISORDERS** **NEUROGENIC PAIN, TINNITUS, AND PARKINSON'S DISEASE.**	
ALPHA: 8-13 HZ **DROWSINESS OR STATES OF RELAXATION.** **DECREASED IN MOOD DISORDERS, CHRONIC PAIN, AND ALL STRESS-RELATED DISORDERS**	
SMR: 12-15 HZ **SUSTAINED IMMOBILITY, AN ACTIVE MIND** **DEPRESSED IN ATTENTION DEFICIT DISORDERS, MOOD DISORDERS, ANXIETY, PANIC, OBSESSIVE-COMPULSIVE DISORDERS, CHRONIC PAIN, AND STRESS-RELATED DISORDERS.**	
BETA: 15-30 HZ **STATE OF FOCUSED ATTENTION OR DURING PERFORMANCE OF NEW AND COMPLICATED MOTOR ACTS** **IRREGULARITIES SIMILAR TO SMR-RELATED DEFICITS**	

Figure 2. Illustration and desciption of theta, alpha, sensorimotor rhythm and beta brain waves (adapted from Peniston & Kulkosky,1999).

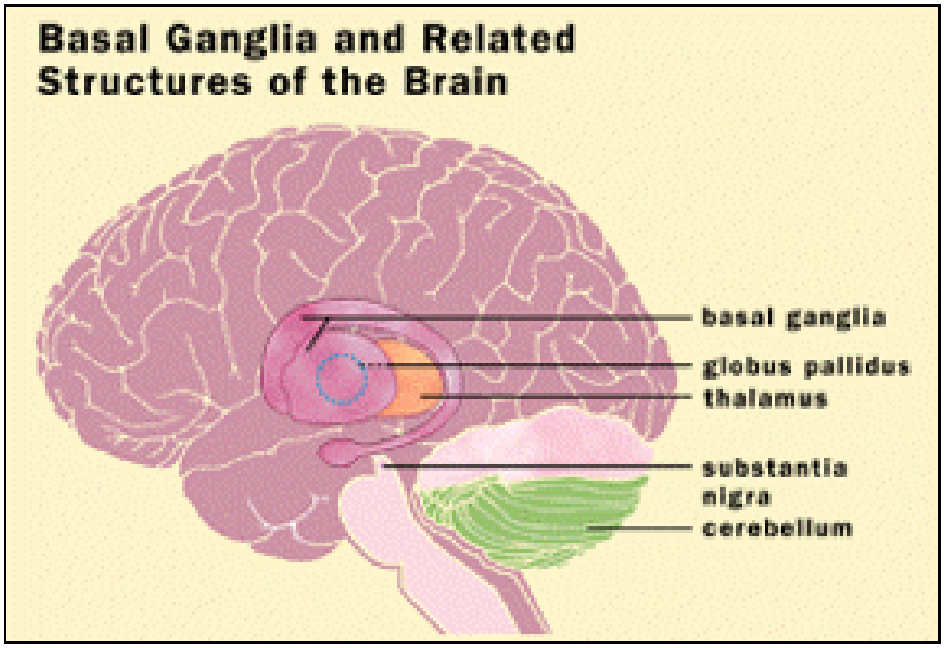


Figure 3. Diagram of basal ganglia and related structures of the brain (adapted from Purves, 1997)

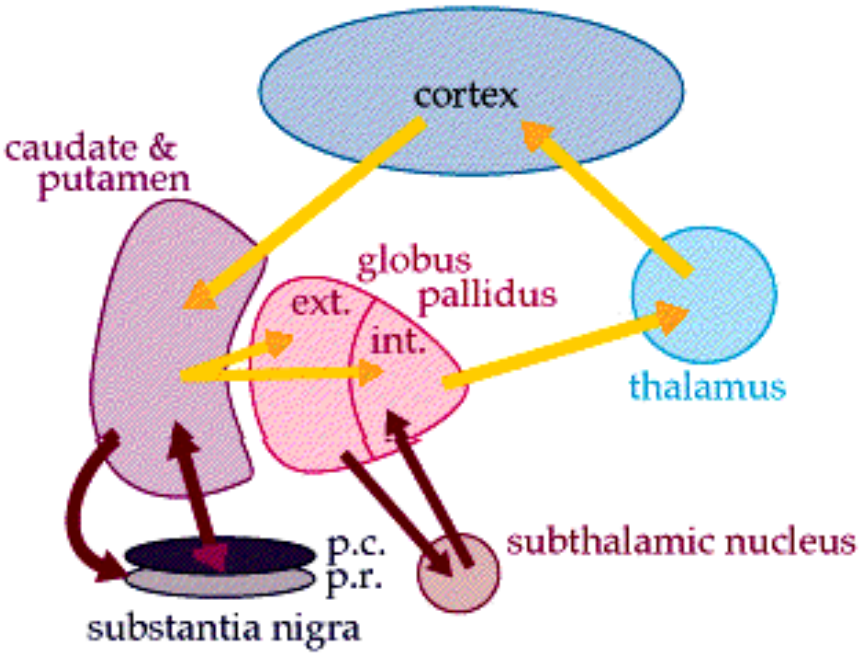


Figure 4. Diagram of basal ganglia structures and thalamocortical pathway (adapted from **http://thalamus.wustl.edu/course/cerebell.html).**

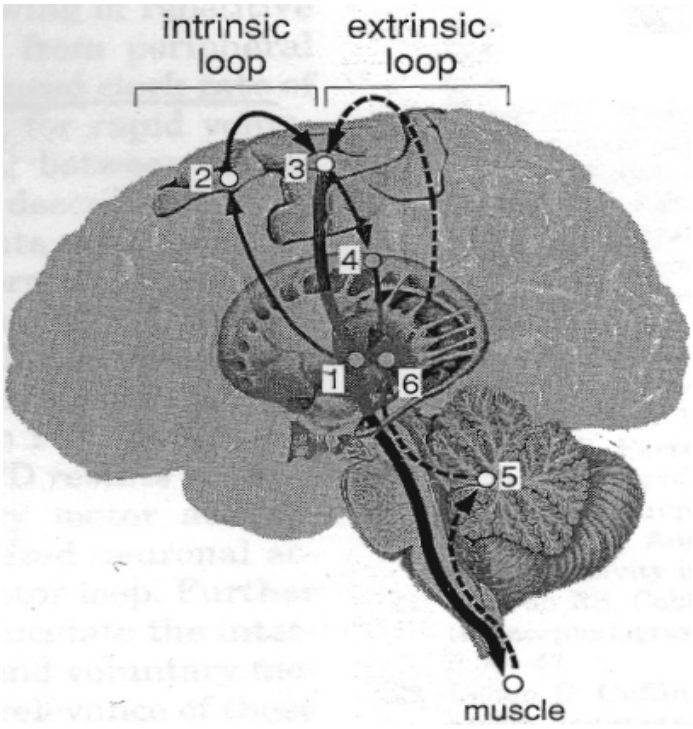


Figure 5. Thalamocortical feedback loops (adapted from Llinas, 1996).

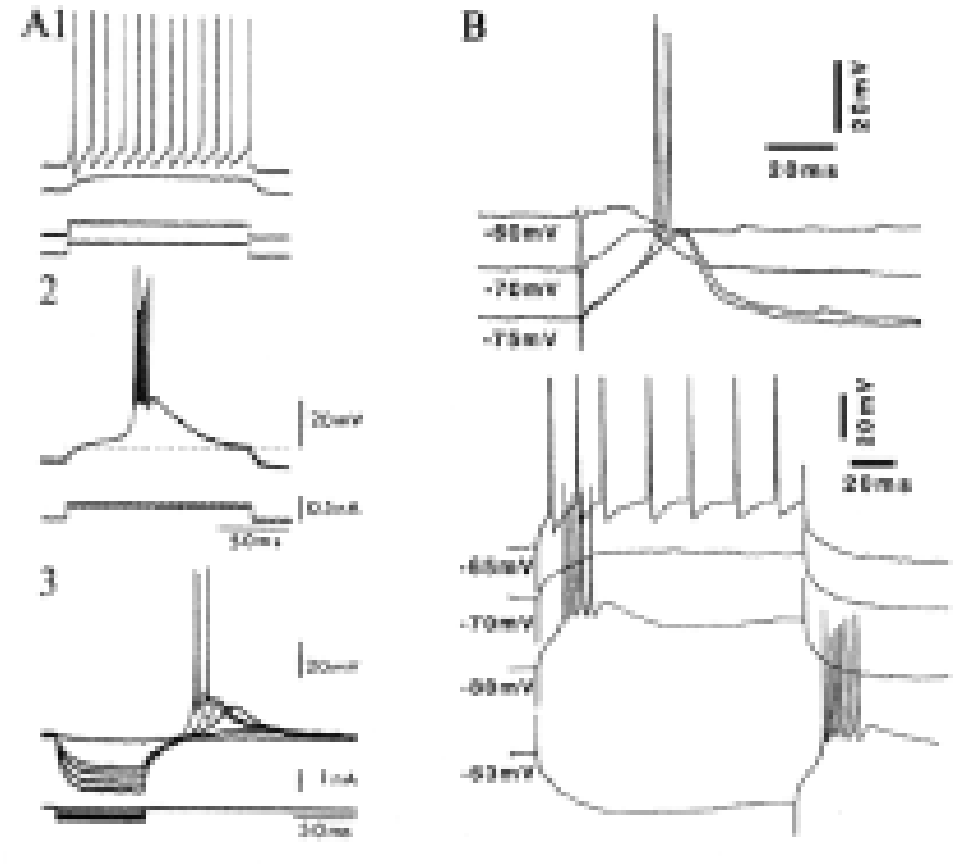


Figure 6. Similarities between the low-threshold spike (LTS) of thalamocortical (TC) neurons *in vitro* and *in vivo*. A) Thalamic neurons recorded from dorsal thalamic slice of guinea-pig, maintained *in vitro*. 1) Subthreshold current pulse (lowest trace) produced a subthreshold depolarization of the cell. The same stimulus, delivered after an imposed depolarization of the cell, produced tonic firing. 2) After hyperpolarization of the cell, current pulse similar to that in (1) produced an LTS crowned by high-frequency burst of action potentials. 3) Rebound LTS also occurred after hyperpolarization pulses of different amplitudes. B) TC neuron from the ventrolateral (VL) nucleus, recorded in vivo. Top three traces depict neuronal responses to stimulation at three different membrane potentials. Bottom four traces show: tonic firing at –65 mV; passive response at –70 mV; spike-burst at –80 mV; and spike-burst at the break of a hyperpolarizing pulse at –63 mV (adapted from Llinas & Steriade, 2006).

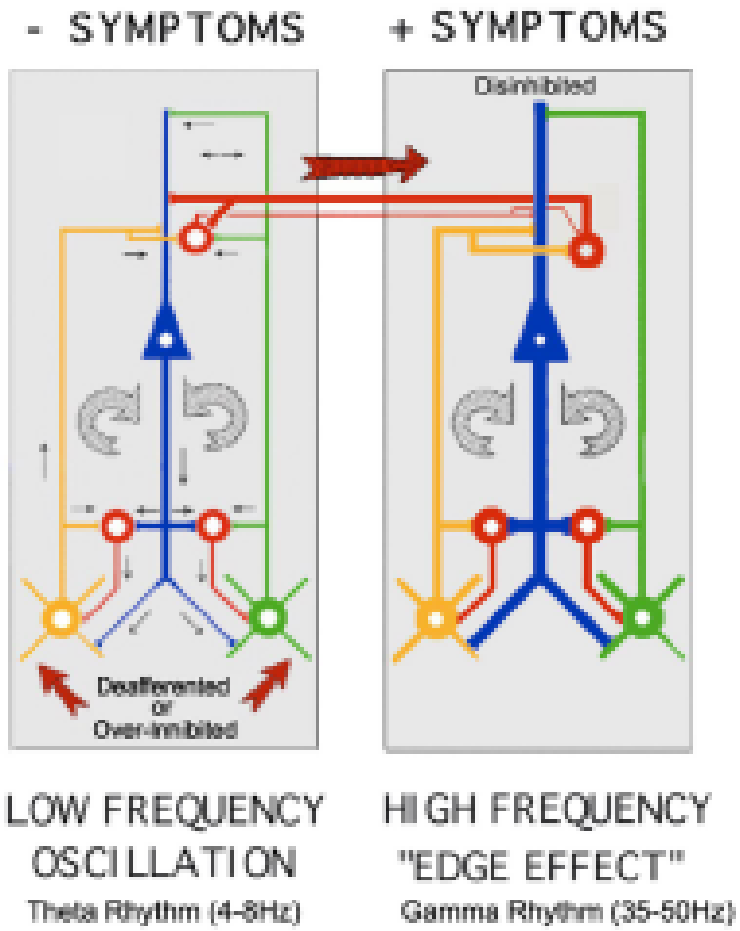


Figure 7. Diagram of the thalamocortical (TC) circuits that support the positive symptoms hypothesis. Two TC systems are shown, the specific pathway (yellow) to layer IV of the cortex that activates layer VI cortical neurons and feed-forward inhibition via inhibitory cortical interneurons (red). Collaterals of these projections produce thalamic feedback inhibition via the reticular nucleus (red at thalamic level). The return pathway (circular arrow on the right) re-enters this oscillation to specific nuclei in later IV pyramidal cells (blue). The second loop shows non-specific nuclei (green) projecting to the most superficial layer of the cortex and giving collateral to the reticular nucleus. The conjunction of the specific and non-specific loops is proposed to generate temporal coherence (left panel). Excess inhibition due to pallidal over-activity (as in Parkinson's disease) hyperpolarizes the cells sufficiently to deinactivate T-type Ca2+ channels resulting in thalamic oscillation at theta-range. Such oscillation can entrain corticothalamic loops (left panel) generating increased coherence as observed in the study by Llinas (2001). At the cortical level, low-frequency activation of corticocortical inhibitory interneurons, by reducing lateral inhibitory drive (disinhibition) can result in high-frequency coherent activation of neighboring cortical modules, causing the edge effect (adapted from Llinas et al., 1999).

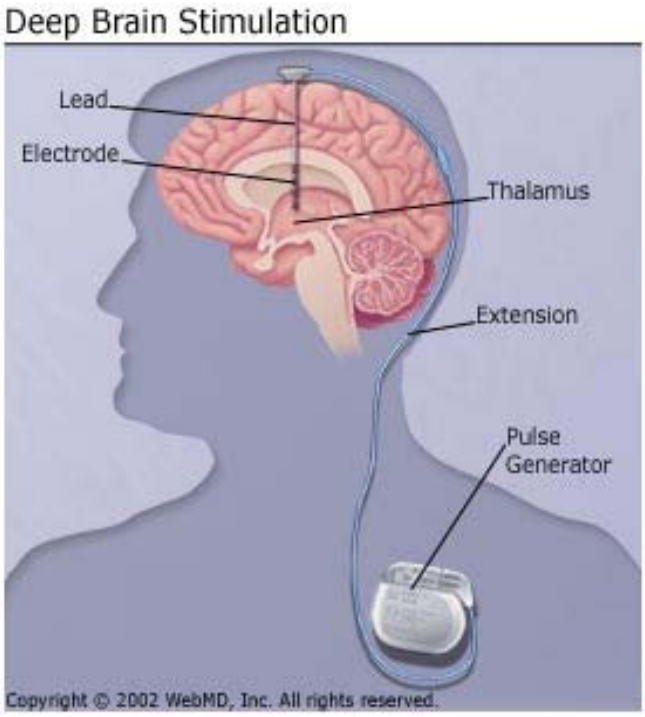


Figure 8. Diagram of electrode placement within thalamic nuclei in deep brain stimulation (adapted from American Parkinson's Association, 2006).

Unified Parkinson Disease Rating Scale (UPDRS)

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability), 0--no disability.

I. Mentation, Behavior, Mood

Intellectual Impairment

0-none
1-mild (consistent forgetfulness with partial recollection of events with no other difficulties)
2-moderate memory loss with disorientation and moderate difficulty handling complex problems
3-severe memory loss with disorientation to time and often place, severe impairment with problems
4-severe memory loss with orientation only to person, unable to make judgments or solve problems

Thought Disorder

0-none
1-vivid dreaming
2-"benign" hallucination with insight retained
3-occasional to frequent hallucination or delusions without insight, could interfere with daily activities
4-persistent hallucination, delusions, or florid psychosis.

Depression

0-not present
1-periods of sadness or guilt greater than normal, never sustained for more than a few days or a week
2-sustained depression for >1 week
3-vegetative symptoms (insomnia, anorexia, abulia, weight loss)
4-vegetative symptoms with suicidality

Motivation/Initiative

0-normal
1-less of assertive, more passive
2-loss of initiative or disinterest in elective activities
3-loss of initiative or disinterest in day to say (routine) activities
4-withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech

0-normal
1-mildly affected, no difficulty being understood
2-moderately affected, may be asked to repeat
3-severely affected, frequently asked to repeat
4-unintelligible most of time

Salivation

0-normal
1-slight but noticeable increase, may have nighttime drooling
2-moderately excessive saliva, hay minimal drooling
3-marked drooling

Swallowing
0-normal
1-rare choking
2-occasional choking
3-requires soft food
4-requires NG tube or G-tube

Handwriting
0-normal
1-slightly small or slow
2-all words small but legible
3-severely affected, not all words legible
4-majority illegible

Cutting Food/Handing Utensils
0-normal
1-somewhat slow and clumsy but no help needed
2-can cut most foods, some help needed
3-food must be cut, but can feed self
4-needs to be fed

Dressing
0-normal
1-somewhat slow, no help needed
2-occasional help with buttons or arms in sleeves
3-considerable help required but can do something alone
4-helpless

Hygiene
0-normal
1-somewhat slow but no help needed
2-needs help with shower or bath or very slow in hygienic care
3-requires assistance for washing, brushing teeth, going to bathroom
4-helpless

Turning in Bed/ Adjusting Bed Clothes
0-normal
1-somewhat slow no help needed
2-can turn alone or adjust sheets but with great difficulty
3-san initiate but not turn or adjust alone
4-helpless

Falling-Unrelated to Freezing
0-none
1-rare falls
2-occasional, less than one per day
3-average of once per day
4->1 per day

Freezing When Walking
0-normal
1-rare, may have start hesitation
2-occasional falls from freezing
3-frequent freezing, occasional falls
4-frequent falls from freezing

Walking
0-normal
1-mild difficulty, day drag legs or decrease arm swing
2-moderate difficultly requires no assist
3-severe disturbance requires assistance
4-cannot walk at all even with assist

Tremor
0-absent
1-slight and infrequent, not bothersome to patient
2-moderate, bothersome to patient
3-severe, interfere with many activities
4-marked, interferes with many activities

Sensory Complaints Related to Parkinsonism
0-none
1-occasionally has numbness, tingling, and mild aching
2-frequent, but not distressing
3-frequent painful sensation
4-excruciating pain

III. Motor Exam

Speech
0-normal
1-slight loss of expression, diction,volume
2-monotone, slurred but understandable, mod. impaired
3-marked impairment, difficult to understand
4-unintelligible

Facial Expression
0-Normal
1-slight hypomymia, could be poker face
2-slight but definite abnormal diminution in expression
3-mod. hypomimia, lips parted some of time
4-masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

***Tremor at Rest**
Face
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

Right Upper Extremity (RUE)
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

LUE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

RLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

LLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

***Action or Postural Tremor**

RUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

LUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

***Rigidity**

Neck
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

RUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

RLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

***Finger taps**

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Hand Movements (open and close hands in rapid succession)**

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Rapid Alternating Movements (pronate and supinate hands)**

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Leg Agility (tap heel on ground, amp should be 3 inches)**

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Arising From Chair (pt. arises with arms folded across chest)**
0-normal
1-slow, may need more than one attempt
2-pushes self up from arms or seat
3-tends to fall back, may need multiple tries but can arise without assistance
4-unable to arise without help

***Posture**
0-normal erect
1-slightly stooped, could be normal for older person
2-definitely abnormal, mod. stooped, may lean to one side
3-severely stooped with kyphosis
4-marked flexion with extreme abnormality of posture

***Gait**

0-normal
1-walks slowly, may shuffle with short steps, no festination or propulsion
2-walks with difficulty, little or no assistance, some festination, short steps or propulsion
3-severe disturbance, frequent assistance
4-cannot walk

***Postural Stability (retropulsion test)**

0-normal
1-recovers unaided
2-would fall if not caught
3-falls spontaneously
4-unable to stand

***Body Bradykinesia/ Hypokinesia**

0-none
1-minimal slowness, could be normal, deliberate character
2-mild slowness and poverty of movement, definitely abnormal, or dec. amp. of movement
3-moderate slowness, poverty, or small amplitude
4-marked slowness, poverty, or amplitude

Schwab and England Activities of Daily Living

Gillingham FJ, Donaldson MC, eds., Third Symp. of Parkinson's Disease, Edinburgh, Scotland, E&S Livingstone, 1969, pp.152-7.

Rating can be assigned by rater or by patient.

*** 100%**-Completely independent. Able to do all chores w/o slowness, difficulty, or impairment.

*** 90%**-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.

*** 80%**-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing

*** 70%**-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.

*** 60%**-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible

*** 50%**-More dependant. Help with 1/2 of chores. Difficulty with everything

*** 40%**-Very dependant. Can assist with all chores but few alone

*** 30%**-With effort, now and then does a few chores alone of begins alone. Much help needed

*** 20%**-Nothing alone. Can do some slight help with some chores. Severe invalid

*** 10%**-Totally dependant, helpless

*** 0%**-Vegetative functions such as swallowing, bladder and bowel function are not functioning.