

Neurofeedback Training in Neurodegenerative Diseases

Ingrid H.C.H.M. Philippens^{a,b}, Brian H. Hallas^b, Joerg R. Leheste^b, German Torres^{b*}

^aDepartment of Immunology, Biomedical Primate Centre, Lange Kleiweg 161, 2288 GJ Rijswijk, the Netherlands

^bDepartment of Neuroscience and Histology, New York College of Osteopathic Medicine of New York Institute of Technology, Old Westbury, NY 11568, USA

Introduction: Why neurofeedback training?

There is a growing interest in neurofeedback training for treating diseases of the brain. Direct training of brain function is an old concept that has re-emerged once again as a potential method through which the brain might be induced to repair itself from traumatic injury or necrotic disease. Indeed, given the fact that innovations in neurological care lag behind other fields of medicine, there is a pressing need to tap into novel therapeutic treatments that target nervous system disorders. However, for decades the field of neurofeedback training has been completely ignored by neuroscientists despite the fact that membrane potential oscillations (i.e., brainwave frequencies) drive the autonomous activity of all neurons. Along the same lines, there is also a large, but healthy skepticism with the premise that training spontaneous electrical activity of one's own nerve cells could repair an ailing brain. Part of the problem is that most neuroscientists still adhere to the treatment strategy of replacing diminished neurotransmitters rather than using the tiny electric currents within a person's neural circuitry to safely and painlessly repair oneself. But this view is rapidly changing. For example, we now know

that the human brain has the capability to rewire itself to some extent: the brain has the ability to spontaneously make new neurons in the hippocampus and in the olfactory bulbs where they form synapses with existing nerve cells to establish functional circuits (Winner et al., 2011). Of significance to neurofeedback training, social experiences can regulate the rate of cell division in the hippocampus and regular physical activity can also increase the birth of new nerve cells in the nervous system (Van Praag, 2009). Furthermore, the human brain is sufficiently plastic to engage the somatosensory system in transmitting high-resolution "visual" information to blind persons (Bach-y-Rita et al., 1969). Thus, it is conceivable that neural connections in the human brain could be induced on demand in a controlled fashion to rewire a specific area laden with injury.

There is also considerable evidence that paraplegics can "regain" some behavioral function when neural or thought signals from the motor cortex are captured while the paraplegic patient tries to move his/her limbs (Dobkin, 2007). This neural signal is then relayed to a receiver computer which eventually executes the thought-motor command. Again, the most remarkable aspect of this concept-of-proof phenomenon is that a paraplegic patient

can control a computer with his/her thoughts to ultimately move his/her disconnected limbs. Against this background, this brief essay discusses the biology of neurofeedback training, points out some of the experimental pitfalls associated with this training technique, and raises the exciting possibility that this thought procedure might provide a strategy to treat Parkinson's disease (PD) through its "rewiring" effects on particular neurons---those that act by releasing the neurotransmitter dopamine.

Neurofeedback training: Background and mechanics

Neurofeedback training (a type of biofeedback) is based on the experimental assumption that all physiological processes can directly be controlled by volitional signals emanating from the nervous system to improve physical or cognitive performance (Miller, 1974). Biofeedback training has its foundations in operant and/or classical conditioning psychology in which precise instruments, superficially attached to the brain, rapidly "feedback" information to the user to modify brainwaves, heart function, muscle activity or skin temperature (Gerber et al., 2007). This operant procedure takes place coherently with real-time, i.e., the feedback provides moment-to-moment information to the user about his/her physiological state with very little delay in between. This phenomenon was first described by Miller in the early 1970's, and subsequently emerged as a data-based clinical practice in which desired physiological processes could be reinforced by an intrinsic, positive "reward" feedback mechanism. Since then, neurofeedback training has been viewed as a potential strategy to self-regulate subjective forms of body sensations, emotional states, thinking patterns and/or psychomotor activities (Heinrich et al., 2007; Reiner, 2008).

Currently, the most widely used neurofeedback strategy is based on quantitative electroencephalogram (EEG) analysis of

spectral (frequency) brainwave content. Essentially, EEG measures the electrical activity generated by the fluctuating summation of excitatory and inhibitory postsynaptic potentials spontaneously generated by the brain (Andriola and Epstein, 1983). To measure brainwave activity through neurofeedback training, electrodes placed above the user's cortex record cycles of pacemaking activity driven by voltage-dependent ion channels. The human cortex is modulated by a group of cells in the thalamus called pacemaker cells and when these thalamic neurons fire action potentials in response to synaptic input, rhythms are produced and recorded as EEG signals on the surface of the brain (Lubar, 1997). By systematically examining the rhythmic, spontaneous firing of action potentials, a specific EEG cortical frequency is correlated with a particular cognitive state (Fig. 1).

Traditionally, the EEG is divided into five different frequencies or spectral bands of neuronal activity – delta (δ ; 0.1-4 Hz) which is correlated with deep sleep, theta (Θ ; 4-8 Hz) which is correlated with drowsiness, alpha (α ; 8-13 Hz) which is correlated with relaxation, beta (β ; 13-30 Hz) which is correlated with alertness and gamma (γ ; 26-100 Hz) which is usually correlated with complex cognitive and motor functions. During neurofeedback training, the most frequently measured spectral signal in the quantitative EEG is the electrical activity of alpha and/or theta banding. As alpha pacemaking, for example, is often correlated with inhibition of electrical activity, it labels visual relaxation above the visual cortex or labels motor relaxation above the motor cortex. A specific activity measured above the sensorimotor cortex is the sensorimotor rhythm (SMR). SMR is restricted to spindle activity over this cortical site and its banding is strongly suppressed during performance of contralateral motor acts or even during motor imagery. Thus, SMR provides a moment-to-moment snapshot of neuronal dynamics which underlie the characteristics of certain sensorimotor functions.

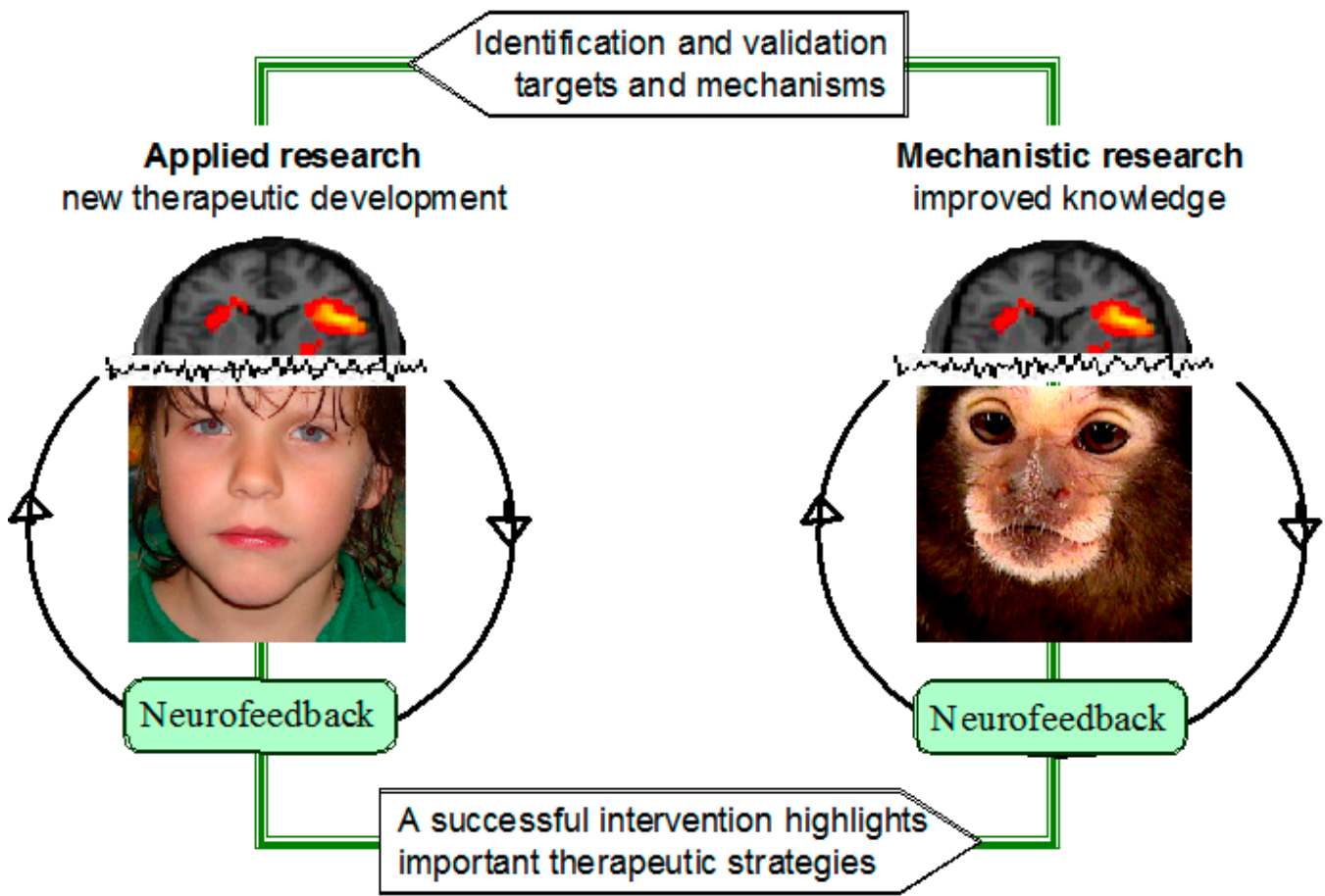


Fig. 1. With increased availability of fMRI technology, real-time brain feedback represents a potentially important avenue for affecting higher-order activity states. Applied (neurofeedback) studies with humans already show the ability of the brain to improve awareness and regulation of one's mental states. Studies with non-human primates (e.g., the marmoset monkey) should help us identify the mechanisms by which the brain imparts motor and sensory plasticity. This translational approach has potential applications to prevention of neurodegenerative diseases and promotion of healthy aging in humans.

Neurofeedback training: Human brain pathologies and experimental pitfalls

The development of a quantitative EEG-based procedure has led to the application of neurofeedback training as adjunct therapy for a number of brain pathologies, including epilepsy (Stodieck and Wieser, 1987; Goldstein, 1997; Egner and Serman, 2006), social anxiety disorder (Moore, 2000; Hammond, 2005), substance abuse (Scott et al., 2002; Trudeau, 2005), insomnia (Jefferys et al., 1996; Cluydts et al., 2006) and attention deficit/hyperactivity disorder (Fox et al., 2005). Although the ap-

plication of neurofeedback training to nervous system disorders appears to successfully improve clinical outcome, lack of appropriate control groups make such findings dubious or invalid to most neuroscientists. More specifically, without appropriate controls, it is difficult to conclude whether significant behavioral changes or improvement in physiology outcome can directly be related to neurofeedback treatment or rather to unspecific factors such as placebo effects or enhanced awareness of the medical condition. It has often been suggested that randomized, double-blinded studies, including a control group of patients with the same symptoms as those undergoing

neurofeedback training should be incorporated to rule out erroneous experimental variables. However, in neurofeedback studies this type of experimental design is rather difficult to implement as baseline values of neuronal activity are spontaneously active even without synaptic input (Drechsler et al., 2007). Therefore, many cognitive and physiological effects attributed to neurofeedback training have little empirical support as they generally lack valid baseline values. Increasing our knowledge about the inner-mechanisms of the brain and the underlying processes of neurofeedback training in a standardized, experimental setting may increase the application of this method to various clinical conditions.

Neurofeedback training: Experimental animals and Parkinson's disease patients

There is limited information on neurofeedback in animals trained under experimental, controlled conditions. The first described animal study explored SMR training in cats more than 40 years ago (Sternman and Egner, 2006). More recently, SMR training was performed in a non-human primate (Philippens and Vanwersch, 2010); the first study to control for erroneous variables such as placebo effects. Together with the availability of non-invasive behavioral test systems for objective quantification of motor function in the marmoset monkey (Philippens et al., 2000) this study showed that non-human primates can also be trained with neurofeedback methods (Fig. 2). Of significant interest, work from the same laboratory has shown that the marmoset monkey is an excellent model system for studying neurodegenerative states, including PD (Philippens et al., 2010). Thus, the well-validated non-human primate model of PD may be useful for determining whether neurofeedback training can improve or perhaps even arrest the damage produced by the absence of dopamine-synthesizing cells in the substantia nigra (see below).

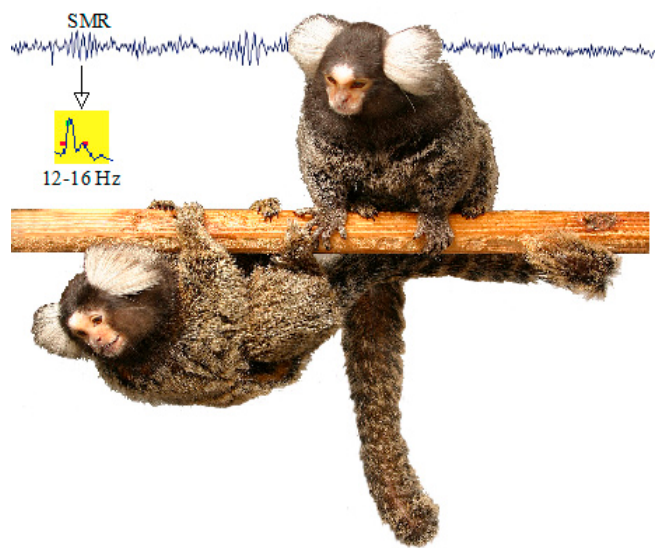


Fig. 2. Free moving marmoset monkeys and telemetric recording of brainwave content. SMR is depicted after on-line, fast Fourier transformation of small epochs of EEG (1.28 sec) into a power spectrum indicating the frequency distribution within one epoch. Power spectra with a peak at 12-16 Hz are positively reinforced by food rewards. This experimental approach raises the possibility that the ability to voluntarily control brain activity (i.e., SMR) improves when it is associated with a stimulus.

As previously noted, SMR is an oscillatory thalamocortical rhythmic pattern of activity with a spectral peak frequency of around 12-16 Hz (Roth et al., 1967). After the identification of this brainwave band, a number of studies were conducted in cats to test the hypothesis of whether SMR training could make these animals less sensitive to epileptic seizures (Sternman and Egner, 2006). Interestingly, SMR training drastically reduced the sensitivity of adult cats to epileptic attacks. Although the exact mechanisms by which SMR training decreases epileptic thresholds in the cat brain are unknown, it is conceivable that changes in certain ion channels reduces the threshold of action potentials in cells generating the epileptic syndrome. To learn more about the underlying mechanisms of neurofeedback training in general or, more specifically, of SMR training, a more complete experimental approach is needed. In this regard, accumulating knowledge about the mechanistic aspects of neurofeedback training is coming largely

from studies of neurophysiology with real-time functional magnetic resonance imaging (fMRI). From these studies, it appears that neurofeedback training modifies the metabolic activity of the human brain, more specifically the striatum (Birbaumer, 2005; Levesque et al., 2005). This finding is of significant interest as the striatum is a region of the brain that is chemically compromised in PD. The critical event in PD is the selective death of dopamine cells in the substantia nigra, a cluster of neurons synaptically connected to the striatum. Progressive loss of these dopamine nerve cells invariably leads to tremors and loss of voluntary movement (Philippens et al., 2010). Dopamine neurons are spontaneously active even without synaptic input and show autonomous pacemaking activity in the nigral-striatal circuit (Chan et al., 2007). In this regard, there is a published study in which a PD patient who underwent SMR training was capable of controlling the involuntary movements caused by the absence of dopamine-synthesizing cells in her brain (Thompson and Thompson, 2002). This finding raises the tantalizing possibility that neurofeedback training could be used as a new, non-invasive strategy to spur brain function in neurodegenerative states. However, a more immediate concern is to further expand the capability of neurofeedback training for gauging a better description of this thought-provoking method, literally.

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Biographies

Dr. Ingrid Philippens (philippens@bprc.nl) received her Ph.D. in neuropharmacology from Utrecht University in 1998 and is currently head of the division Neuropathology at the Biomedical Primate Research Centre (BPRC) in the Netherlands. She has been awarded several research grants from the Dutch Ministry and US organizations (DTRA, USAMRMC). Most of the grants were focused on neuroprotection. Her specific research interests are centered on amelioration or prevention of neurodegeneration, such as Parkinson's disease, with the focus on translational research.

Dr. Brian H. Hallas (bhallas@nyit.edu) received his Ph.D. in neurobiology from Purdue University in 1979. He also holds an M.S. in biology from Purdue University, a B.A. in Psychology, and a B.S. in Biology from University of Hartford. He has been awarded numerous research grants and has authored many articles in scientific journals. He is the recipient of various honors and awards, most recently the prestigious Presidential Service Award from New York Institute of Technology in 2007. In 2004, he was awarded a fellowship by the Heritage Foundation Health Policy for Research in Health Policy based on stem cell research. From 2003 to 2007, he was Associate Dean of Research at the New York College of Osteopathic Medicine of New York Institute of Technology, where he is currently Chair and

Professor of the Department of Neuroscience and Histology. He has published over 70 peer reviewed articles, several book chapters and 225 abstracts.

Dr. Joerg R. Leheste (jleheste@nyit.edu) received his Ph.D. in Molecular Biology from the Humboldt University, Berlin/Germany in 2001. He also holds an M.S. in Biology with focus on Molecular Genetics and a B.S. in Biology from Philipps University, Marburg/Germany. Dr. Leheste is currently employed as an Assistant Professor in the Department of Neuroscience and Histology at the New York College of Osteopathic Medicine of the New York Institute of Technology. His specific research interest focuses on age-related disease of the central nervous system. Dr. Joerg Leheste has published numerous articles in peer reviewed journals and is supported by grants from The New York College of Osteopathic Medicine.

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Neuroscience and Histology at the New York College of Medicine of New York Institute of Technology. His specific research interests are centered on the biological basis of mental disorders.

Contact Information:

Corresponding Author: German Torres, Ph.D.
Associate Professor
Department of Neuroscience NYCOM/NYIT
PO Box 8000
Old Westbury, NY 11568 USA
Telephone: 516-686-3806
Fax: 516-686-3750
E-Mail: torresg@nyit.edu



Editor's Column

It is late spring here in Florida as I write this column. The weather here has been beautiful for several weeks, but unlike some parts of the

country, we need rain badly. We have seen several unusual events in the world recently, some seemingly for the better and some not so. Bin Laden was finally located and killed about a month ago. The great Mississippi river and several others have recently flooded and destroyed many homes and much farmland. Joplin, Missouri was hit a few days ago by the worst, most destructive tornado perhaps in US history. We are about to start hurricane season here, and an active season is predicted. A volcano is once again disrupting air traffic in Europe. In Japan, the nuclear catastrophe is still unfolding. However, the world did not end on April 21 (or the rapture take place) as Harold Camping predicted, but seemingly unfazed, he has now predicted that the world will end on October 21. Anyway, we have time to prepare (or party, as the case may be). In spite of all the natural and man-made catastrophes, we must not lose site of the good things going on; the outpouring of assistance to those who have been affected by nature and man, the apparent turn-around in the world economy and the great land in which we in America live. We should all take an active part in helping each other in whatever way we can.

This issue of the *Carrier* is a very interesting one. Brian Hallas, German Torres and their colleagues have presented a look at neurofeedback training in neurodegenerative diseases. Their article comes at a time when there is increased excitement in the neuroscience community about the possibilities of computer-human interfaces and in transmission of motor information via computer to

disconnected neural tissue controlling limb movements. Recently, news stories ran in papers and national news about a group at UCLA and the University of Kentucky who has had some success in generating standing and walking movements in a paraplegic man. Our Neuroscience colleague, Reggie Edgerton was one of the leaders of this group. They implanted an array of electrodes over the lumbar spinal cord of the man and were able to provide adequate stimulation to the cord to initiate standing and walking movements. The plasticity of the brain and spinal cord are just beginning to be realized and we can look forward to much more in the future as this type of research continues. Indeed, we in the Neuroscience community have seen great progress in the past 10 years and I feel that we are just at the beginning of the upward curve as new knowledge, building on the foundations of past research and combined with new technologies and computing power are brought to bear on both the understanding of how the nervous system functions and how to treat seemingly intractable human conditions. We indeed live in exciting times.

David Kopf Instruments is the world leader in stereotaxic and related instruments for the Neuroscience community. They have sponsored the Kopf *Carrier* since 1973, making it the oldest such newsletter in at least the neurosciences, if not in all fields. We have published articles on a great variety of subjects, ranging from neuroethics to neurohistory to various data related studies. The articles are the property of the authors and are posted online at the Kopf website. www.kopf-instruments.com. All past *Carrier* issues are available there. I welcome all of you to consider writing an article for the *Carrier*. Articles can be on any topic of interest to the Neuroscience community and should be referenced appropriately. If necessary, Kopf Instruments will assist with graphics and other features of the article. If you have an interest in submitting an article, please contact me at drmikep@earthlink.net.

We look forward to seeing you at the Society for Neuroscience meeting in the fall. David Kopf Instruments will be located at booth 1625.

Michael M. Patterson, Ph.D.

Science Editor

David Kopf Instruments

954-288-5518

954-452-6812 (FAX)

drmikep@earthlink.net