8-2003

Tomographic neurofeedback : a new technique for the self-regulation of brain electrical activity

Marco Congedo

To the Graduate Council:

I am submitting herewith a dissertation written by Marco Congedo entitled "Tomographic neurofeedback : a new technique for the self-regulation of brain electrical activity." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

Joel F. Lubar, Major Professor

We have read this dissertation and recommend its acceptance:

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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We have read this dissertation
and recommend its acceptance:

Michael R. Nash, Professor

John W. Lounsbury, Professor

William L. Seaver, Professor

Accepted for the Council

Vice Provost and Dean of Graduate Studies

Tomographic Neurofeedback; a new Technique for the Self-Regulation of Brain Electrical Activity

A Dissertation
Presented for the
Philosophy Doctor Degree

The University of Tennessee, Knoxville

Marco Congedo
August 2003

Ancora devi compiere i tre anni,
e la tua saggezza non ha paragoni,
né la tua pazienza conosce tentennamenti.
A te dedico questo lovoro,
Aaron,
mio bellissimo Pasha.

Acknowledgments

This Dissertation is the fruit of my work at the University of Tennessee during the past four years, henceforth all individuals who have been surrounding and supporting me during this time have been contributing somehow to this endeavor of mine. I will have to mention only a few of them, handing my apologies to the many others.

I found in Dr. Joel Lubar, my major professor and advisor, an exceptional mentor. I own to him all I know in electrophysiology, because he shared with me his knowledge and he left me all the space I needed for pursuing my studies by myself, always with encouragement, enthusiasm, and never with envy.

With Dr. Michael Nash and Dr. John Lounsbury, other two members of my committee, I could enjoy a sincere friendship beyond the professional work. After talking with them I am always left with very good feelings.

Dr. Seaver, the member of my committee from the Department of Statistics, has been always open, available and helpful. As far as I know, in the whole University, he was the only one with whom I could share my interest in permutation resampling.

Dr. James Schmidhammer definitely instigated in me the passion for Statistics. I've always been fascinated by Statistics, but after I took three courses from him, I started *enjoying* Statistics.

This project would not have been possible if it was not for the contribution of David Joffe, an engineer currently working at Lexicor Medical Technology, Inc., Boulder, Colorado. David voluntarily wrote an essential piece of software for the implementation of current density neurofeedback. His expertise in the neurofeedback field and his knowledge of the Neurosearch-24 machine (Lexicor Medical Technology, Inc.) was invaluable. Indeed David created that machine many years ago and instructed the machine to send via serial port four channels of real-time information, including the intra-cranial current density of interest. I meet David only a few times, but I always remind him as a wonderful man.

Similarly, the project would not have been possible if it was not for Dr. Roberto Pascual-Marqui, to whom I own most of what I know of his beautiful creature, LORETA, and to whom I own my switching from old-fashioned Pascal to Delphi Pascal Programs.

Jassee Rothove, an undergraduate student trained in the Brain Research and Neuropsychology Laboratory of the University of Tennessee, has been constantly involved in the experimental part of this Dissertation and corrected all the original manuscript. Besides his very good work, he brought in the lab his friendship, creativity and kindness, brightening all our days.

My very good friends, Youssef, Les, and Cem, all stood by me in the high and fall of the vicissitudes of my life with warm and loyalty. To them I own my happiness. Cem actually contributed to this research answering questions on mathematics and helping me in the study of the feedback function we employed. Indraneel came in my life recently, but in very little time he changed it very much. The citation in the preface was extracted from a book that he presented to me.

The eternal unconditioned love of my mother, Amelia, now almost 70-years-old, never stops to make me wonder.

Abstract

A major limitation of the current neurofeedback paradigm is the limited information provided by a single or a small number of electrodes placed on the scalp. A considerable improvement of the neurofeedback efficacy and specificity could be obtained feeding back brain activity of delimited structures. While traditional EEG information reflects the superposition of the electrical activity of a large number of neurons, by means of inverse solutions such as the Low-Resolution Electromagnetic Tomography (LORETA) spatially delimited brain activity can be evaluated in neocortical tissue. In this Dissertation we implement LORETA neurofeedback, we introduce a new feedback function (Φ^1) sensitive to dynamic change over time, and we clarify several issues related to the learning process observable with neurofeedback. The reported set of three experiments is the first attempt I am aware of to prove learning of brain current density activity.

Three individuals were trained to improve brain activation (suppress low Alpha (8-10 Hz) and enhance low Beta (16-20 Hz) current density) in the anterior cingulate gyrus cognitive division (ACcd). Participants took part of six experimental sessions, each lasting approximately 30 minutes. Randomization-Permutation ANCOVA tests were conducted on recordings of the neurofeedback training. In addition a randomized trial was performed at the end of the treatment. During eight two-minutes periods (trials) participants were asked to try to obtain as many rewards as they could (4 "1" trials) or as few rewards as they could (4 "0" trials). The order of trials was decided at random. The hypothesis under testing was that participants acquired volitional control over their brain activity so to be able to obtain more rewards during the plus condition as compared to the minus condition.

We found evidence of volitional control for two subjects ($p=0.043$ and $p=0.1$) and no evidence of volitional control for one of them ($p=0.271$). The combination of the three p-values provided an overall probability value for this experiment of 0.012 with the additive method and 0.035 with the multiplicative method. These results strongly support the hypothesis of volitional control across the experimental group. Trends of the Beta/Alpha power ratio in the ACcd were in the expected direction for all the three subjects, however the combined p-values did not reach significance.

With as few as six training sessions, typically insufficient to produce any form of learning with scalp neurofeedback, the experiment showed overall signs of volitional control of the electrical activity of the ACcd. Possible applications of the technique are important and include the treatment of epileptic foci, the treatment of specific brain regions damaged as a consequence of traumatic brain injury, and in general of any specific cortical electrical activity.

Preface

...Work done with anxiety about results is far inferior to work done without such anxiety,

in the calm of self-surrender. Seek refuge in the knowledge of Brahman.

They who work selfishly for results are miserable...

(Bhagavad-Gita, ancient Sanskrit Hindu sacred poem)

The human brain is the most functional and complex system we know. Not only, despite our little knowledge of this complexity, we could not imagine a system exceeding it. The most advanced spaceship created by man, the proud of our well endowed science, fondly appears like a trivial toy, so fragile, heroic, and mechanic, as soon as we wonder at the astonishing realizations of the animated mind. With more synapses in the human brain than stars in the milky way, for any single neuron is connected with thousands of peers in both the ingoing and outgoing directions, where any two neurons can communicate through a myriad of alternative paths in an electromagnetic net of prodigious complexity, Satan himself could not do a better job in puzzling the desire of knowledge of the mankind. The faculties of the human mind, sensation (intuition), emotions, intellect, desire (affection: pleasure-pain, drives), will, consciousness (self-reflection), gender polarization, are the unsolvable mysteries of the greatest of all mystery, to which we give on the whole the name of *life*.

Our "knowledge" of the mind is a heap of sand in the oceans. It does not matter if we try to understand it organically, physically, spiritually, or according to any other suitable frame of knowledge. According to the organic approach, basically "ignorant" we were 150 years ago, when phrenologists dominated the scene pretending to portion the brain like a cake in specialized areas, and substantially ignorant we are still today, despite the advances in the technique of investigation, which have been truly impressive. It is characteristic of our time the almost universal assumption of "functional specialization". According to this assumption higher

cognitive functions have a preferred anatomical localization that can be isolated and defined. Virtually all neuroimaging studies using PET, fMRI, SPECT, electromagnetic tomography, etc. are conceived within this paradigm. I am not surprised then to review the massive literature and find a large inconsistency among experiments. Although we have been successful in correlating many cognitive functions to anatomical and physiological processes, or at least to individuate brain regions more involved than others in a defined cognitive function or clinical condition, any attempt to establish a clear and universal relationship has been in vain. New fields of research emerged lately sparkling from different conceptions. Among others, chaos theory and neural networks. These and other efforts are a reaction to the dominant paradigm, clearly insufficient and inadequate, actually not that far ahead from the naïve thought of the phrenologist.

Even the idea to delimitate cognitive functions is questionable, since, the definition and delimitation of a cognitive function or of a clinical condition is already a catastrophic reduction of complexity. Not less important is the eternal question whether the intelligence can be auto-intelligent, that is, if it can acquire cognition of itself at all. According to the German philosopher Immanuel Kant there are intelligible domains and non-intelligible domains of the *existent*. Even admitting the complete analytic comprehension of the organic functions of the brain, nevertheless unthinkable today, we would not resolve our blindness to spiritual substances; and the two terms of the soul, matter and spirit, intelligence and body, are only the two faces of the same entity. To say it as Krishnamurti did in a different occasion, they are the *shadow* of each other. According to Indian wisdom they, like all conceptual and sensorial opposites of our life (e.g., love-hate, pleasure pain, cold-heat) are illusions; they are boundary of the life in this dimension, storms in the mind of the seer, who can reach peace only in the union with the Supreme Being: the *Brahman*. That is the original *source* of all dimensions of reality, of which our Universe is just one of the many instant manifestations. In my undergraduate thesis at the University of Padova, Italy, while working in social cognition, I recognized in the concept of *Universe* the outmost category in which all existents can be included. This is the most comprehensive entity in which we do admit ourselves as part of it. What I meant is that *all* of us possess, clearly or obscurely (without an act of consciousness), the *intuition* of the Universe. This has to be true for all existents. Furthermore this intuition is of the same nature as the intuition of ourselves, although the latter is available much more readily, and probably also in greater extent. The means of *experience* are the faculties of the human mind I mentioned above.

The reason why medical science proceeds so steadily thanks to endless funds is the fear of death, or the desire for life, again, two undistinguishable opposite terms. Advances in the medical science successfully increase the average life expectancy. Regardless, the nature always finds for itself means of expression of the *universal destiny* (karma). The contemporary recrudescence of lethal viral diseases (so far AIDS and SARS have been of concern) greets our ignorance of the life, and makes fun of us, while we struggle like pigs for staying in the farm instead of visiting the slaughterhouse. Nonetheless science itself is the greatest endeavor of the mankind. True science is super-human. Devoid of bias (objective), like a Platonic idea, it shines bright and clear in the court of reality and speechless beauty. Actual science made a different history though, as we all know.

Having an idea in mind, in my practice I found useful to diverge from the original goal, to probably come later on the same problem with renewed perspectives. Maybe. In this sense, for the benefit of all of us, I see for the scientific community great enlightenment outside the scientific realm and in the non-scientific community great enlightenment in the scientific realm. This dissertation is nothing more than a grain of sand in the ocean, a nullity to which I pretend to give some importance, for there is no achievement without a spirit carrying it out, and there is nothing closer to the Supreme Being then ourselves.

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Introduction

The dissertation will try to unify two distinct fields of research in the electromagnetic neurosciences, electroencephalograpic (EEG) biofeedback and Low-Resolution Electromagnetic Tomography (LORETA). EEG Biofeedback (neurofeedback) is a technique used in behavioral medicine as un adjunct to psychotherapy. An electronic device records EEG activity at a particular scalp location, extrapolates physiological measurements from the signal and converts it to a visual and/or auditory object dynamically co-varying with the brain signal. For example, the length of a bar in a graph may vary continuously as a function of voltage. The process is real-time, that is, the object continuously represents brain activity with a minimum delay (< 500 milliseconds) held constant. Typically, over 20 to 40 sessions of thirty minutes each, spaced two-three days apart, the subject acquires possible awareness about the signal and learns how to shape it in a desired direction, which leads to a modification of brain electrical activity. Research in this field started in the late 1960s (e.g., Engstrom, London, & Hart, 1970; Nowlis & Kamiya, 1970; Travis, Kondo & Knott, 1974). While first attempts aimed to acquire control over the posterior dominant rhythm (8-13 Hz, known as "alpha"), recently the application of the technique is mainly clinical. Several successful protocols have been established for the treatment of Attention Deficit Disorder (Barabasz & Barabasz, 1996; Linden et *al*, 1996; Lubar, 1991, 1997; Lubar & Shouse, 1976; Tansey & Bruner, 1983), Unipolar Depression (Rosenfeld, 2000), and Epilepsy (Lubar & Bahler, 1976; Lubar et *al*, 1981; Sterman, 1973, 1981; Swingle, 1998). For other disorders such as Traumatic Brain Injury (Thatcher, 2000; Thornton, 2002), Anxiety Disorders (Moore, 2000), and Chronic Fatigue Syndrome (James & Folen, 1996; Hammond, 2001) research is in progress.

The most appreciable qualities of neurofeedback are that it is non-invasive and that it requires an active role on the part of the patient. In some cases a neurofeedback training can completely replace the use of psychoactive compounds. This quality makes it a preferred choice especially in the case of children and adolescents, individuals for which the balance of neurotransmitters and the brain anatomy are still in formation. The major limitation of neurofeedback resides in the limited information provided by a single or a small number of electrodes placed on the scalp. The EEG is given by the measurable potential difference between the active electrodes and a reference (neutral) location. It is known (Nunez, 1995; Nunez &

Silberstein, 2000) that the EEG signal reflects mainly the superposition of the electrical activity created by the ionic charge oscillation (due to postsynaptic potentials) around the pyramidal cells found in the neocortex. The signals from a large population of neurons beneath the electrode are superimposed to create the measurable EEG. Put differently, the response of the electrode is *spatially unspecific*. Another limitation is the inconsistency resulting from the choice of the reference electrode placement. No reference is truly inactive, and different reference locations result in the measurement of different electric fields. A considerable improvement in the neurofeedback technique could be obtained if it were possible to consider spatial-specific brain activity and if the issue of the chosen reference could be resolved.

LORETA (Pascual-Marqui, 1995, 1999a; Pascual-Marqui, Michael, & Lehmann, 1994) is currently the most popular inverse solution technique. It has been extensively used in electrophysiological research (e.g., Bosch-Bayard et *al*, 2001, Isotani et *al*., 2001; Pizzigalli et *al*., 2001; Pascual-Marqui et *al*, 1999) and has been evaluated independently in several laboratories (e.g., Fernández-Bouzas, et *al*., 1999; Fuchs, Wagner, Köhler, & Wischmann, 1999; Gomez & Thatcher, 2001; Prichep, John, & Tom, 2001; Worrell et *al*., 2000). LORETA estimates the distribution of electrical neuronal activity in 3-dimensional space, basing the estimates on a dense grid of electrodes placed over the entire scalp. While EEG is a measure of electric potential differences, LORETA estimates the current density that results in measurable potential difference, i.e., the source of the observed electric field on the scalp (EEG). Co-registering the solution to a brain atlas (Lancaster et *al*., 1997, 2000; Talairach, & Tournoux, 1988; Towle at *al*., 1993) it is possible to map electrical activity in all cortical structures. Such a functional imaging technique, like Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), is called tomography. While traditional EEG information is limited to the scalp activity, by means of inverse solution brain activity can be evaluated intracranially. The reconstruction is independent of the reference used in obtaining the EEG recordings (Pascual-Marqui, 1999a). This is another distinctive advantage of LORETA over scalp EEG, which depends on the reference, enabling a superior consistency in results obtained across laboratories.

The aim of this dissertation is to explore the use of LORETA current density data for neurofeedback. This has never been done before. With this dissertation we hope to motivate the research for more powerful neurofeedback techniques. Potential benefits from this method are considerable. First, deep cortical structures could be trained. In scalp EEG the activity generated

by these structure is underrepresented, since the EEG signal primarily registers activity of the more superficial structures. Second, delimiting in 3D space the cerebral region trained may enable faster and more specific learning. For example, in our pilot studies we focused on a subdivision of the anterior cingulate, called *cognitive division* (Bush et *al*, 1999; Devinsky, Morrell, & Vogt, 1995), which functions makes it distinct from the *affective division* of the anterior cingulate, an anatomical structure laying just inferiorly. Such specificity is not possible with scalp EEG neurofeedback. Possible applications of the technique include the treatment of epileptic foci, the treatment of specific brain regions damaged as a consequence of traumatic brain injury, and in general of any specific cortical electrical activity. Of course, the technique is interesting per se, not only for its clinical application. Fields that in the future may be using tomographic neurofeedback include virtual reality and thought-based device control. Recent advances in remote detection of human EEG using ultrahigh input impedance sensors (Harland, Clark, & Prance, 2002) let us foresee in the near future a myriad of technological implementations. For the moment being, in order to establish clinical usefulness, we need to verify whether current density can be enhanced or suppressed as it is for scalp potentials, whether current density training is faster or slower than scalp potential training, and whether the physiological and behavioral changes correlated with current density training are comparable to those obtained by means of scalp potential training. This dissertation is a first step in this direction.

The research also involves a theoretical and technical investigation of neurofeedback. The theoretical study will focus on the feedback signal returned to subjects as sensory information. We will be employing a mapping function that has never been conceived before. This function is independent of subjective characteristics of brain fields and is sensitive to dynamic changes. Regarding the technical aspects of the research, we wrote a computer program for data processing, feedback delivery, and data analysis. This research has been carried out in co-operation with David Joffe, an engineer working in Boulder (Colorado) who wrote a complementary program for real-time LORETA data acquisition. Finally, in this study we will establish a statistical methodology based on randomization-permutation theory (Blair and Karnisky, 1994; Blair, Troendle, and Beck, 1996; Edgington, 1995; Holmes, Blair, Watson, & Ford, 1996; Karnisky, Blair, & Snider 1994; Lunneborg, 2000; Manly, 1997; Nichols, & Holmes, 2001; Pesarin, 2001; Westfall, Young, 1993) for the Type I error combination of learning curves

(single-subject time series) and randomized trials. These issues are here consistently introduced and constitute another novelty for the neurofeedback literature.

Chapter 1 reviews technical, theoretical, physiological and methodological aspects of the Low-Resolution Electromagnetic Tomography (LORETA). The interested reader will find in this chapter a concise introduction of the LORETA method and its physiological interpretation. Chapter 2 introduces the neurofeedback concept, presents methods for overcoming the difficulties encountered while generating LORETA neurofeedback and illustrates the Φ^1 function, the new feedback signal function we employ. The chapter also discusses relevant issues implicated in the learning process associated with neurofeedback, proposes a classification of different learning processes that can be attained, and introduce a statistical framework for the combination of single-subjects learning curves and randomized trials. Chapter 3 illustrates the actual experimental procedures and equipment used to generate LORETA neurofeedback and reports the experimental studies we have conducted. Readers familiar with LORETA may skip chapter 1. Those uninterested to unessential details about the LORETA method may skip section (1.1). Our original work is exclusively contained in chapters 2 (methodological and theoretical) and 3 (technical and experimental).

Chapter 1

Low-Resolution Electromagnetic Tomography (LORETA)

1.1 Definition of the Problem

Electromagnetic tomographies allow for the 3D non-invasive localization of the electro/magnetic activity of the brain. Reconstruction methods are generally termed inverse solutions (Sarvas, 1987). Here we are interested in the inverse solution of the EEG and particularly to the class of instantaneous, 3D, discrete, distributed, linear solutions for the EEG problem. Such methods do not assume a limited number of dipole sources in the brain, but directly compute a current distribution throughout the full brain volume, hence they are more in line with available knowledge in brain electromagnetic physiology. For our experimental studies we chose the best known among such methods, the Low Resolution Electromagnetic Tomography, or LORETA (Pascual-Marqui, 1995, 1999a,b; Pascual-Marqui et al., 1994).

The forward EEG problem is

$$\Phi = \mathbf{K} \cdot \mathbf{J} \qquad (1.1.1)$$

In (1.1.1), Φ is a $n \cdot 1$ matrix comprised of n scalp electrical potential differences (Microvolts),

$\mathbf{J} = (\mathbf{j}^T_1 , \mathbf{j}^T_2 , .. , \mathbf{j}^T_m)^T$ is a $(3m) \cdot 1$ matrix comprised of m current densities components (Micromperes) parallel to the x, y, and z axis $\mathbf{j}_m = (j_{xm} , j_{ym} , j_{zm})^T$. The superscript "^{T}" denotes transpose.

$\mathbf{K}$ is a $n \cdot (3m)$ transfer matrix, with α^{th} row, α: (1..n), given by $(\mathbf{K}^T_{\alpha 1} , \mathbf{K}^T_{\alpha 2} , .. , \mathbf{K}^T_{\alpha m})$, where $\mathbf{K}_{\alpha\beta} = (k_{x\alpha\beta} , k_{y\alpha\beta} , k_{z\alpha\beta})^T$ is the lied field (Malmivuo and Plonsley, 1995).

Let also $\{\mathbf{s}_1, \mathbf{s}_2, .., \mathbf{s}_n\}$ be the 3-dimesional coordinates of the measurement points (electrodes), and $\{\mathbf{v}_1, \mathbf{v}_2, .., \mathbf{v}_m\}$ the 3-dimensional coordinates of a discrete regular grid of source points within the brain volume (cubic regions called voxels). Both **s** and **v** are in Cartesian space. Knowing $\boldsymbol{K}$, **J**, **s**, and **v**, the forward problem is straightforward, in the sense that it allows a unique solution.

EEG measurements Φ are known. $\boldsymbol{K}$, **s**, and **v** can be modeled with sufficient approximation by means of appropriate head models (Cuffin and Cohen, 1979; Cuffin et al., 2001; Hämäläinen and Sarvas, 1987; Towle et al., 1993). On the other hand **J** is unknown.

The Inverse EEG problem is therefore stated as

$$\hat{\mathbf{J}} = \boldsymbol{T} \cdot \Phi \qquad (1.1.2)$$

In (1.1.2), $\boldsymbol{T}$ is some $(3m) \cdot n$ generalized inverse of the transfer matrix $\boldsymbol{K}$ satisfying the measurements in forward equation (1.1.1) (Campbell and Meyer, 1979). Problem (1.1.2) is known to have infinite solutions, so that there exists an infinite number of $\boldsymbol{T}$'s resulting in distributed estimations of current densities $\hat{\mathbf{J}}$ that satisfy the measurements Φ.

Many approaches have been tried to find the "best solution" to the inverse problem (1.1.2). Some sort of constraint is usually applied in order to solve the problem. LORETA enforces maximal smoothness. A Laplacian smoothness operator selects the distribution of current density for which, at every single voxel, the current density is as close as possible to the average current density of the nearest neighbors. Weighted averages are allowed, and "neighborhood" is also non-unique, that is, the size of the neighborhood can be defined quite arbitrarily. The result is a method with little localization error and low spatial resolution such that, if the source is point-like, the reconstruction is blurred (Fuchs et al., 1999; Pascual Marqui, 1995, 1999a; Pascual Marqui et al., 1994). Formally, LORETA minimizes

$$\{\|\Phi - \mathbf{K}\,\mathbf{J}\|^2 + \lambda \|\boldsymbol{A}^2\,\mathbf{J}\|^2\} \qquad (1.1.3)$$

where

$\|\Phi\text{-}K\,J\|^2$ is the error of fit,

A^2 is a discrete laplacian operator

and λ is the weighting factor that LORETA evaluate at the limit to 0.

For technical details on the LORETA method consult Pascual-Marqui (1995, 1999a, 1999b) and Pascual-Marqui et *al.* (1994).

1.2 LORETA Advantages and Disadvantages

Current knowledge in the literature and in our own studies allows us to draw the following conclusions. We will express them in terms of advantages and disadvantages of the LORETA method:

Advantages:

- Localizations of local maxima have, on the average, little error.
- The method is truly capable of deep localization.
- The method does not assume a limited number of dipolar point sources.

Disadvantages:

- The current density estimation cannot be easily extended to nuclear subcortical regions.
- Source reconstruction is "blurred" no matter what the spatial extension of the original source.
- The deeper the source the more blurred the current density reconstruction.
- The depth of superficial sources is overestimated.
- The method is very sensitive to physiological artifact contaminating the EEG (Oculogram (OCG), electromyographic activity (EMG) of the facial muscles, tongue etc. etc) and to noise in general.

In addition to the advantageous characteristics of the LORETA method, we mention here the advantages of ET in general

- Is a High Temporal Resolution Technique.
- Is a non-invasive technique.

1.3 Current Density

The simplest statistical quantity we are typically concerned with is the current density module (inner auto-product of the three dimensional current density vector) $\sqrt{\breve{y}}$

$$\sqrt{\breve{y}}_{(v)\aleph} = \| \hat{\mathbf{J}}_{(v)\aleph} \| = \sqrt{[\hat{J}^2_{(v)x\aleph} + \hat{J}^2_{(v)y\aleph} + \hat{J}^2_{(v)z\aleph}]} \qquad (1.3.1)$$

or its square

$$\breve{y}_{(v)\aleph} = \| \hat{\mathbf{J}}_{(v)\aleph} \|^2 = \hat{J}^2_{(v)x\aleph} + \hat{J}^2_{(v)y\aleph} + \hat{J}^2_{(v)z\aleph} \qquad (1.3.2)$$

For any given fourth dimension $\aleph$ (see next section), the current density at voxel with coordinates **v** is expressed by the square root of the sum of the squares of the three current density moments on the x, y, and z basis. This is the elemental physical quantity considered in all previous studies with LORETA. The current density module (CDM) $\sqrt{\breve{y}}$ (1.3.1) for a particular $\aleph$ can be graphically conceived as the length of a vector in a three-dimensional space. In summary, we ignore the orientation of the vector and study its *length* only.
The physiological meaning of this quantity is treated in a subsequent section (1.5).

1.4 The Fourth Dimension and the Domain Shift

In (1.3.1) and (1.3.2) subscript "$\aleph$" denotes the fourth dimension of the measurements. In reality this dimension is the time, so that for each of *m* voxels, $\sqrt{\breve{y}}_{\aleph}$ forms stochastic positive only time series over the recording period. For continuously recorded EEG typical recording

periods consist of 3-5 minutes. The signal is sampled and converted into digital format with sample rate typically in the range of 64-1024 samples per second. The inverse solutions apply to any instant in time, hence the high-resolution property of EEG/ET, in contrast to the poor temporal resolution of PET and fMRI. By means of Discrete Fourier Transform (Beauchamp, 1973; Brillinger, 1975) the time dimension can be shifted into the frequency domain. Actually its more computationally efficient version FFT (Fast Fourier Transform) is employed. One does not need to estimate 3-D FFT for each of the m time series of $\hat{\mathbf{J}}$. It is known that an equivalent result is obtained considering the (Hermetian) cross-spectral matrix $\mathbf{\Omega}$ of the scalp potential differences (Φ) (Gomez and Thatcher, 2001). The $(n \cdot n \cdot \omega)$ cross-spectral matrix $\mathbf{\Omega}$ is essentially the variance-covariance matrix of the complex Fourier coefficients. It is comprised of ω variance-covariance matrices, one for each of the ω dicrete frequencies. Remember that there are n scalp measurement points. In practice, for any given discrete frequency ω, the corresponding spectral current density, i.e., the current density in the frequency domain, is given by (Frei et *al.*, 2001):

$$\hat{\mathbf{J}}^{\omega} = (\boldsymbol{T} \cdot \mathbf{\Omega}^{\omega} \cdot \boldsymbol{T}^{\mathrm{T}})^{\backslash} \qquad (1.4.1)$$

where the superscript "\" means "diagonal elements"

Off-diagonal elements of $(\boldsymbol{T} \cdot \mathbf{\Omega}^{\omega} \cdot \boldsymbol{T}^{\mathrm{T}})$ contain information about the cross-spectral current densities, the analogue of the covariance in the time domain. Those objects allow the estimation of coherence (Nunez et al., 1997) between voxels, a very powerful measure of synchronicity (often interpreted as the degree of communication) between different brain regions. Such a challenge has been undertaken by Pascual-Marqui (2000, personal communication). For a given EEG segment of t measurement samples, ω is equal to $t/2$ and the frequency resolution is given by 1/#secs, where #secs are the number of seconds composing the segments. For example, for a segment 256 samples long with sample rate=128 samples per second, there will be 256/2=128 discrete frequencies ω, starting at ½=0.5 Hz e progressing in ½ Hz increment up to the folding frequency (64 Hz). Typically $\mathbf{\Omega}$ is estimated as the average of the cross-spectral matrices computed on the available (artifact-free) EEG segments. A rectangular window is applied to EEG segments before entering the FFT algorithm.

EEG segments are termed epochs and are typically comprised of 2 to 8 seconds. Given periodicity (a condition not exactly matched by EEG data) a collection of time series and their Fourier transform are identical, in the sense that one can always shift from one domain to the other preserving the signal intact. Therefore we see that $\sqrt{\breve{y}}_{N}\ (m)$ refers to the CDM of a particular voxel (in 3-D space) composing vectors comprised either of t instants time (time domain) or of ω dicrete frequencies (frequency domain). When EEG is recorded continuously during rest or experimental tasks, data is usually analyzed in the frequency domain (FD LORETA). This reduces complexity considerably (there are thousands of time instants but only tens of discrete frequency) and links result to the physiological knowledge about EEG rhythms. We also use FD LORETA to study the consistent (long-term) changes in current densities following neurofeedback training. In this case baseline EEG recordings enter a pre-post design. When stimulus-locked repeated trials of potentials are averaged (ERP: Evoked Response Potentials), the time domain (TD LORETA) is more easily manageable while the shift in the frequency domain is of little theoretical usefulness, since what matters then is the time-locked processing of a simple cognitive element (a visual or auditory constant stimulus). For training neurofeedback purposes the CDM is continuously estimated in real-time small time windows. We wish to retain frequency specific information as well. As a matter of fact, successful neurofeedback training is always frequency-specific. For this application we need to band-pass filter the EEG signal in real time and then compute the LORETA CDM in the time domain. Since the signals have been filtered this represents a frequency-specific information. However the high time resolution is preserved. This is the method we employed in our LORETA neurofeedback experimental studies. It allows the processing of the largest possible amount of information. We name it frequency-specific time domain LORETA (FTD LORETA).

1.5 Electrophysiology of Electromagnetic Tomographies

Little is known about the physiological meaning of current density estimation. The brain, and especially the neocortex, is an extremely interconnected organ. The typical path between any two cortical regions has been estimated to be only two or three synapses. Electrical fields as registered through the scalp are largely due to the postsynaptic potential of neocortical cells

(Nunez, 1995), in particular pyramidal cells. Pyramidal cells are organized in adjacent columns normally oriented (perpendicular to the tangent of the local neocortex surface) Because of their morphology and physiology, they act as (ionic) parallel dipoles rhythmically inverting the polarity that is formed in the basal and apical portion of the pyramidal cell. Considering a small enough volume, if pyramidal cells contained there were to fire independently, the linear superposition of their moments would cancel out at any instant time and we wouldn't be able to record any EEG from the scalp. Instead we would observe random noise. The spontaneous EEG signal, all over the cortex, is oscillating according to the superposition of both random and periodical components, with the latter being significant, as indicated by periodograms and autocorrelation functions. This suggests that adjacent pyramidal cells not only fire simultaneously, but also synchronously (in phase) according to harmonic periods. This fact, known theoretically and verified by means of intracranial recordings, is the justification of the maximal smoothness constraint applied by LORETA. The smoothness constrain is justified also by the fact that, except for seizures discharges, focal electrical activity is generally not recorded at the scalp (Nunez and Silberstein, 2000), thus it is of little sense to reconstruct them.

EEG frequencies below about 50 Hz are believed to reflect the modulation of synaptic action fields around their background level (Nunez, 1995). The energy of the EEG signal above 50 Hz is very low and is seldom investigated. Furthermore the skull and the scalp act as low-pass filters and cut out most high-frequency activity. Current within cortical tissue consists of movement of ions positively and negatively charged in opposite directions, but there is no total charge in any large enough tissue volume. Given this state of affairs, the scalp potentials have been related proportionally to the number of cells acting synchronously, and inversely proportional to the square root of the number of asynchronous cells. Although this seems closer to a fact than to a speculation, useful physical models of current density able to explain the underlying physiology and its behavioral correlates have not been discovered yet. As a consequence applied research with EEG/ET seldom results in a true insight about the topic of interest. Poor explicative power is nowadays a common and unfortunate characteristic of all functional imaging modalities, and not only of EEG/ET. While EEG/ET are high-temporal resolution techniques with low spatial resolution, Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) have low temporal resolution and high spatial resolution. These complementarities are the spur of much research in functional modalities integration (e.g., Babiloni et al., 2000). Each modality has its own characteristics for both it

concerns the nature of the data and the underlying physiological process that are measured. Functional data from hemodynamic/metabolic techniques (PET, fMRI) and electromagnetic techniques (EEG/ET, EMG/MT) are not necessarily correlated although some correlation exists. For example Leuchter et al.(1999) found the oxygen metabolism to be positively correlated with energy in δ(0-4 Hz), θ(4-8 Hz) and high β(>18 Hz) frequency range, but negatively correlated with α(8-13 Hz) bands. Nunez and Silberstein (2000) note that while hemodynamic and metabolic measures are believed to increase with neuronal firing rate, EEG/EMG signatures increase as a function of synchrony only, thus an increase in firing rate may well result in a smaller electromagnetic scalp field. We see that the interpretation of ET findings is always tentative, and that the empirical investigation is still the more secure path. This is true also for EEG, PET, and fMRI.

1.6 An Actual Implementation

In the LORETA-Key implementation of the LORETA method (Pascual-Marqui, 1995), the current density is estimated for each of 2394 voxels with resolution 7x7x7 mm. The solution is restricted to gray matter for theoretical reasons. Gray matter, white matter and subcortical structures have different resistances and therefore the appropriate head model would increase in complexity. Admitting that such a model is formalized, we know that most of the electrical activity recordable from the scalp is generated in the neocortex (Nunez, 1995). It makes little logical sense to estimate generators for which the signal is very low and overwhelmed by signal referring to other sources. Nevertheless such an approach has been followed by the group in Cuba (Bosch-Bayarsd et al., 2001). The method is known as VARETA, standing for Variable Resolution Electromagnetic Tomography. A data-driven smoothness operator is implemented so that smoothness is applied locally. In general, the deeper the source, the less the "visibility" of the source from the scalp, the more the smoothness is required in order to obtain localization. The author is not aware of a published point spread function simulation using VARETA. In the LORETA implementation each voxel has been labeled as gray matter (including part of Hippocampus and of the Amygdala, and the entire Cingulate gyrus) according to anatomical labels defined in the Talaraich and Tournoux atlas of human brain (Talairach and Tournoux, 1988). The atlas has been computed from 305 MRI recordings and is virtually the standard in

functional neuroimaging (e. g., it is most used in PET and fMRI). A mask is applied to the reconstruction space (called the volume). A voxel is included in the space if its probability to be gray matter is bigger than 0.33 *and* if its probability to be gray matter is bigger than the probability to be white matter or cerebrospinal fluid. LORETA-Key implements a three shell spherical model (skin, skull, and cortex) co-registered to the MRI atlas of Talairach and Tournoux (1988). Anatomical labeling of each grid point is then possible (Lancaster et al., 1997, 2000; Talairach and Tournoux, 1988). The co-registration used realistic EEG electrode coordinates reported by Towle et al. (1993).

1.7 Applied Research

LORETA is by far the most popular Electromagnetic Tomography (ET). It has been used in a variety of both clinical and experimental researches. Also, LORETA has become a standard against which new ET are confronted (Grave De Peralta Merendez et al., 2001). Among others we report the following:

Pizzigalli and associates (2001) investigated the involvement of the anterior cingulate in the response to treatment of depressed patients. Worrell and associates (2000) localized epileptic foci in patients with medically intractable partial epilepsy with symptomatic brain lesions documented by MRI. Winter and associates (2001) used LORETA to compare the positive 300 ms. (p300) auditory ERP in normal controls and schizophrenic patients. Jaušovec and Jaušovec (2001) investigated the difference in both auditory and visual ERP's between high and low intelligence individuals. MDMA (methyenedioxymethanphetamine) effects on the current density of human brain have been explored by Frei and associates (2001). Isotani and associates (2001) investigated the source current density during hypnotically induced anxiety and relaxation states. Lehmann and colleagues (2001) studied the source current density of an advanced meditator during volitionally self-induced altered state of consciousness. Fernández-Bouzas and colleagues (1999) combined CT scans and VARETA to test the hypotheses that EEG delta activity is associated with brain lesions, while EEG theta activity is generated in the vicinity of edema. Prichep, John, and Tom (2001) used VARETA to localize a deep white matter lymphoma and confirmed results with MRI. Pascual-Marqui and colleagues investigated brain abnormalities in

first-episode schizophrenics (1999). For a comprehensive review of LORETA applied research see Pascual-Marqui et *al.* (2002a, 2002b).

1.8 Recent Developments

While we where carrying out this study Pascual-Marqui (2002) published an improvement of the LORETA method, called Standardized Low-Resolution Electromagnetic Tomography (sLORETA). The method is based on the regularization (standardization) of the minimum norm inverse solution proposed by Hämäläinen and Ilmoniemi (1984). The method achieves zero localization error in point spread function simulations. Blurring is comparable to other competing published inverse solutions (Pascual-Marqui, 2002), although, as compared to LORETA, sLORETA could reconstruct sources with more blurring when less then 32 electrodes are used (Pascual-Marqui, 2003, personal communication).

sLORETA sets a new standard in the class of instantaneous, 3D, discrete, distributed, linear solutions. No improvement is possible as far as localization is concerned. Further improvements may concern only the amount of blurring. The advantage of using such a method instead of LORETA in tomographic neurofeedback is currently under investigation.

1.9 Implications for Tomographic Neurofeedback

Limitations of the LORETA method have been listed in section 1.2. Here we review them and we discuss their implications for Tomographic Neurofeedback. Clearly, at the present stage nuclear subcortical regions cannot be trained. As compared to LORETA, sLORETA relaxes smoothness border conditions. As a result, sLORETA enables the reconstruction of current density distribution in the case of a non-connected grid. Although subcortical regions can now be in principle visualized, the amount of information contained in real-time EEG still does not

suffice for this purpose because the contribution of subcortical regions to scalp potentials is negligible.

The blurring and localization error of LORETA can be considered constant when noise, deepness of the source, and geometry of the head are constant. For the same human subject, once the region to be trained is specified and given that electrodes are positioned in the same locations at each session, all these factors are approximately constant. Henceforth their incidence on the validity of LORETA neurofeedback training is negligible. For instance, in neurofeedback training the consistent change over time of some electrophysiological parameter in a specified region is of interest. If such a change appears then the protocol is considered successful. Our experimental unit is a single subject and is subjected to repeated measurements. In order to treat statistically the changes over time we only need the instrument to be internally valid. Averaging measurements in the region to be trained reduces the impact of the blurring effect. The bigger the region, the better the reduction. Localization error is also reduced as a function of the extent of the region. For what it may concern any of these factors, while imprecision is introduced in absolute terms, in relative terms it is irrelevant. In other words, while raw measurements are affected, the ratio between any two measurements is not. This point will be illustrated with an example. Suppose a specific portion of the left frontal lobe is to be trained. This is our target region, which later we will refer to as the region of interest (ROI). Current density is averaged within the region at each instant of time. We are interested in the (relative) changes over time in these measurements. Because of localization error, individual head geometry, electrode placement etc. the anatomical target region we would like to train will be slightly different from the actual region of the brain that is trained. Nevertheless changes as measured over time reflect real changes in the actual region. Given these considerations it is important in clinical application of LORETA neurofeedback to select the ROI according to some objective criterion. For example, the subject's electromagnetic tomography could be compared to a large normative database (Congedo & Lubar, 2003), so to individuate regions where the deviance from the norms is significant. Alternatively the subject could perform a cognitive task to establish statistically what part of the brain is interested in accomplishing the task.

We also notice that extra-cranial artifacts and excessive noise in general invalidate LORETA inverse solutions. Ironically, by restricting ourselves to the use of as few electrodes as 19 we achieve minimization of intra-cranial noise. In fact the more electrodes we use the more

smoothness LORETA requires as seen by a "leave-one-out" kind of cross-validation (Pascual-Marqui, 1999b; Pascual-Marqui, 2003, personal communication) Instead extra-cranial artifacts pose a serious problem. Since artifacts are not constant over time their impact on the validity of the current density estimation is great in both absolute and relative terms. In other words, because of artifacts, changes over time may not be due to a consistent change in the trained region, but to change in extra-cranial artifacts. Therefore great care should be undertaken in order to inhibit the feedback display when artifact contamination is present. The solution we adopted to solve this problem is explained in detail in the next chapter.

Chapter 2

LORETA Neurofeedback

2.1 Definition of the Problem

Figure 1 (see Appendix I for all Figures and Tables) is a schematic representation of the neurofeedback process. Traditionally, neurofeedback is based on scalp EEG. A specified parameter is extrapolated from the continuously recorded EEG forming a real time signal, which we will refer to as the physiological signal (PS). For example, the scalp voltage at a particular electrode may be band-pass filtered in the alpha range (8-12 Hz). The PS might be the absolute magnitude of the filtered EEG. A visual or an auditory object will co-vary with the PS forming a continuous feedback signal (CFS). For example, the pitch of a continuous tone may vary proportionally to the alpha magnitude. The subject continuously receives feedback as sensory information (Figure 1A). Over a certain number of neurofeedback sessions the subject acquires awareness of the underlying process and becomes able to shape the CFS. Since the CFS co-varies with the PS, shaping of brain physiology actually occurs. In Figure 1A the yellow question mark indicates the uncertainty about the actual brain region contributing to the scalp voltage. In tomographic neurofeedback the PS is given by the current density in a specified intra-cranial region of interest (ROI). All the remaining parts of the process are the same. Tomographic neurofeedback is represented schematically in figure 1B. In the picture the ROI is colored in yellow and corresponds roughly to a portion of the anterior cingulate. The CFS is now a function of the current density and co-varies with it.

Soon after the first published reports, biofeedback evoked a great interest among scientists and practitioners (Lynch, 1973; Pinelli, 1975; Schwartz, 1973). Neurofeedback as an application of biofeedback to the brain stands out as the most exciting challenge. Since then most research in neurofeedback has been carried out in north America. Lately there has been increasing interest in Europe (e.g., Egner and Gruzelier, 2001; Hardman et al., 1997; Vernon et *al.*, 2003). Neurofeedback requires dedicated and sophisticated equipment. The field advances with the

advance in technical instrumentation allowing the realization of more powerful paradigms and new paradigms as well. In this dissertation we present the first implementation of tomographic neurofeedback. Yoo and Jolesz (2002) explored functional Magnetic Resonance Imaging neurofeedback. The group in Tuebingen directed by Niels Birbaumer is currently using the same technique (Strehl, personal communication).

2.2 Advantages of the Tomographic Neurofeedback in General

There are al least three distinct advantages of the tomographic neurofeedback as compared to the scalp (traditional) neurofeedback:

1. Deep cortical structures can be trained.
2. The ROI is a special-specific region.
3. The physiological signal (PS) is independent from the reference used to record the scalp potentials.

We now discuss these advantages in more details. The EEG is given by the measurable potential difference between the active electrodes and a reference (neutral) location. Most of the EEG signal as recorded on the scalp reflects the superposition of the electrical activity created by the ionic charge oscillation (due to postsynaptic potentials) between the apex and the base of the pyramidal cells found in the neocortex (Nunez, 1995; Nunez & Silberstein, 2000). The further the distance from the electrode, the less a neuronal region contributes to the signal. Nonetheless a large population of neurons beneath the electrode will be superimposed to create the measurable EEG. We see that scalp potentials provide a *spatially unspecific* piece of information. With scalp neurofeedback it is virtually impossible to train a relatively small brain region selectively and discretely. If the ROI is deep we cannot avoid training also the regions found in between the ROI and the active electrode. Actually, more superficial regions will contribute to the PS more than the target ROI. As an example, suppose we wish to train the portion of the anterior cingulate depicted in Figure 1B as a yellow area. In SN we would place the active electrode approximately as depicted by a green disk in figure 1A. Although we are interested in the anterior cingulate only, we cannot help the training of the medial and superior frontal gyri located anteriorly and

superiorly to the ROI. Even if the ROI is superficial, scalp neurofeedback does not allow the training to be specific on that region only. With tomographic neurofeedback the ROI can be as spatially delimited so to be as little as a single voxel (a few cubic millimiters) and, regardless of its depth, can be trained selectively without affecting any other brain region. The spatial specificity and the ability to be applied to deep cortical structure enables targeting that was otherwise impossible. This may results in more efficient protocols in clinical settings in that it may enable the research to find more efficacious protocols for particular clinical conditions and make present protocols more effective.

The reference-independence property of LORETA is more than a mere technical issue. What an active electrode records is the potential difference between that location and the location where we apply the reference electrode. Changing the location of the reference electrode changes the PS. LORETA current density estimation is the same for any choice of common cranial reference (Pascual-Marqui, 1999a). Results across laboratories are more easily consistent because of this property. In the EEG and neurofeedback field consistence of procedures and methods are an important issue and it is our opinion that, for the sake of the field, much effort should be undertaken to enhance it.

2.3 Continuous and Discrete Feedback

Traditionally, neurofeedback has been conceived as an *operant conditioning* technique (Lubar, 1991; Sterman, 1981). In this view the neurofeedback is a tool for behavior modification. However, early research in the field stressed the *self-regulation* aspect of the process (Hardt & Kamiya, 1976). This duality conceals the little knowledge we have about the learning process associated with neurofeedback and plays an important role in formulating precise experimental hypotheses. This discussion is necessary for the understanding of our choice of experimental designs and will be reconsidered in section (2.7). As a matter of fact, over a number of training sessions human subjects can learn to shape their brain activity in a desired direction. Yet how this might happen is unknown. Figure 2 will help illustrating the difference between the operant condition conception and the self-regulation conception of neurofeedback. In Figure 2 the yellow area superimposed onto the brain indicates the target region of the brain (ROI) from which the PS

is extracted. Stochastic oscillation of current density will provide a PS (indicated in red). In Figure 2 the CFS is of the visual kind and is represented by a green bar displayed on a computer screen. The height of the bar co-varies in real-time (with a minimum delay < 500 msec) with the PS. The subject may be asked to try to increase or to decrease the size of the bar. Feedback information reaches the eyes and is transmitted to the visual sensory structures of the brain. For simplicity we represent the perceptual process with the primary visual cortex only. At this stage of investigation it is not essential to consider the entire process of visual perception. The dotted arrow connecting the primary visual cortex and the ROI closes the loop. The question mark nearby reminds us that what happens in between the *perception* of the object and the *volitional* effort to shape the brain electrical activity is unknown. Notice at this point that both perception and volition are believed to be conscious acts. So far we encountered exclusively conscious processes. The dotted gray line represents a threshold for the height of the bar such that, any time the PS rises above the threshold a discrete feedback signal (DFS) is delivered. This may be given in the form of a discrete auditory beep or as the flesh of a led light. Sterman's training of sensorimotor rhythm (SMR) in cats (1973) and most work with neurofeedback makes use of DFS in addition to CFS or replaces the latter entirely with DFS. When discrete feedback is delivered any time that a "reinforcement" condition is met (e.g.,"PS above the threshold") the paradigm of neurofeedback resembles the operant conditioning. In this case the learning process might take place even outside of conscious awareness and, in theory, could be enforced even against the person's will. In 1976 Hardt and Kamiya suggested that the DFS is not as effective as the CDF. They accused manufacturers of neurofeedback equipment to favour the DFS paradigm for simplicity of construction. In these authors' view, the learning process implies a volitional act.

According to the over thirty years' experience in EEG and Neurofeedback of Dr. Lubar (personal communication) a key factor in deciding the success of a neurofeedback training is the individual's *motivation.* In a way, the neurofeedback process can be seen as a way to acquire a certain degree of control over a physiological process (brain electrical activity) of which typically we do not have control and of which we are not aware if not for the *conscious effect* it produces on us in the form of emotions, feelings, sensations, impressions, thoughts, and pain. Hereafter by motivation we mean the volitional effort to achieve a result, and not the drive. In this sense motivation belongs to consciousness and is synonymous of *will.* Kotchoubey and colleagues (2002) found that subjects were able to correctly estimate changes in their brain activity, corroborating the hypothesis that by means of neurofeedback human subjects acquire a certain

awareness of their own brain processes. In other words, the control exercised upon a quantifiable phenomenon (electrophysiology) appears to be volitional. In our experimental studies we made use of both continuous and discrete feedback signals. However instead of limiting ourselves to measures of learning that could have been taking place outside a volitional act, we designed a randomized trial to ascertain if our subjects actually acquired *volitional control* over their brain activity. That is, if after the training were they able to shape their electrical activity at will. With this study we would like to stress the role of motivation in the success of neurofeedback training. How such a volitional act may succeed in enforcing underlying electrophysiological processes remains an open issue of the utmost importance to the scientific community.

2.4 Extra-Cranial Artifacts

In section 1.8 we discussed the pernicious influence of extra-cranial artifacts on LORETA images. While it would be extremely difficult to control every source of EEG contamination, three of them, eye movements, eye blinks and facial muscle contractions, need to be meticulously monitored. Eye movements and blinks produce spurious large slow potential in the frontal electrodes. Facial muscle contractions include neck, forehead and jaw muscles contractions. They produce noisy and "spiky" fast activity with power peak typically above 40 Hz. They are better seen in the electrodes close to the interested muscle group. While forehead and neck tension is usually easy to manage and the subject can be helped in relaxing these muscles, jaw tension is sometimes persistent. Jaw tension tends to be continuous and may constitute a serious problem for neurofeedback training. Depending on the person, several relaxation techniques can be tried so to achieve muscle quiescence. One of them is simple and typically effective; the subject concentrates on his/her own breathing while relaxing comfortably with the eyes closed. As far as a valid procedure for tomographic neurofeedback is sought, we need to set up at least two *inhibit filters* (IF) and stop the feedback process as soon as the artifacts contamination of the EEG is no longer negligible. If the neurofeedback process is not stopped in the presence of artifacts, the subject may learn to produce those artifacts whose quantitative characteristics simulate the targeted brain activity to be rewarded. For example, if the protocol consists in enhancing high frequency activity in a frontal location, the subject will soon discover that tensing the forehead is the easiest way to achieve the goal. Even without intention, he or she

will learn to produce artifacts instead of meaningful changes in brain activity. As Dr. Sterman once said (personal communication): "Nowadays we train the EMG, not the EEG!". Next, below we explain the methods we used for settings the two IF, called EOG IF (Electro-oculogram Inhibit Filter) and EMG IF (Electromyogram Inhibit filter).

Since eye movements and blinks produce potentials of abnormal magnitude the EOG IF can be based on raw scalp voltage. The maximum of the absolute voltage at electrodes FP1, FP2, F7, F8, F3, and F4 (10-20 system), is computed in real time. Eye blinks and eye movements are better seen in one of these electrodes. As soon as the maximum exceeds a fixed *threshold*, the IF is turned ON and the neurofeedback process is stopped. When this happens the activity of the IF is signaled to the subject by means of, e.g., a flashing light on the computer screen. Once the maximum falls below the threshold the IF is turned off after a short delay (1 sec.), and the neurofeedback resumes. Eye movement and especially eye blinks cannot be avoided when the subject undertakes the training with the eyes open. Subjects are usually instructed to blink two-three times in a row anytime they feel the need. Then they can keep the eyes still for some 20 seconds and concentrate for that period of time. In our experience we found that these directions are easily managed. Blinks do not pose a serious problem for eyes-open neurofeedback. A more serious problem is the use of contact lenses. When wearing contact lenses the eyes tend to dry up more rapidly. In most individuals the dryness causes irritation. The subsequent pain disrupts the concentration of the subject.

For experimental purposes the threshold for the EOG filter should be set at the beginning of the training during a preparatory session and never change afterward. While the subject watches the computer screen the maximum across the 6 electrodes is monitored. The threshold is set so not to interfere with the training when the subject is not blinking or moving the eyes in an appreciable manner, and at the same time, to set the IF on as soon as the subject blinks or moves the eyes sharply. Using software with adequate real-time monitoring capabilities this task requires only a few minutes, and the threshold can be kept as it is for the entire training.

Muscle tension usually does not produce large potentials. However, by monitoring the autospectrum and autocorrelation of the EEG, it is possible to recognize it. One could build sophisticated EMG IF and the efforts would not be unrewarded. Both scalp voltage and LORETA current density can be used for this purpose. The solution we adopted is simple, yet effective. In order to define the physiological signal (PS) the current density within the ROI is extracted in

some band-pass of interest. In addition we extract it for the 35-55 Hz band-pass. In this frequency window EEG power is little as compared to EMG power. Because of technical limitations our low-pass filter for EEG acquisition was set to 64 Hz. Around 60 Hz all North American EEG acquisition devices implement a notch (cut out) filter to suppress disturbance from the power supply net. Ideally the low-pass filter should be set at 100 Hz or more and the extended 35-100 Hz band-pass should be employed to detect muscular activity. As for the EOG IF, the threshold for the EMG IF is set at the beginning of the training during a preparatory session. While the subject watches the computer screen the 35-55 Hz band-pass current density and his/her real-time EEG are both monitored. It is important to make use of two screens, one showing the EEG and the other monitoring current density activity. The threshold is set to not interfere with the training when the subject is not producing appreciable EMG as it should be seen momentarily in the raw EEG. At the same time the threshold has to be chosen to set the EMG IF on as soon as the subject's EMG is no longer negligible. Evidently considerable expertise with human EEG is required to set the threshold. The technician or the experimenter should be an individual well-trained in EEG and should be able to recognize EMG activity as it appears on cranial electrode. Of course the use of EMG cheek, neck, and forehead electrodes would be useful at this stage to set the threshold. Then, during actual neurofeedback sessions these extra-electrodes become mostly unnecessary.

Unlike eye movements and blinks, physical characteristics of the EMG are not quiet constant over time. On different days the average background EMG activity can be quiet different reflecting the subject's general bodily and psychic tension. The behavior of the chosen threshold should be monitored during several sessions. The tomographic neurofeedback training should be always performed while a technician screens the real-time EEG. In this way he/she can make sure that excessive muscular activity sets ON the filter, while at the same time the filter does not switch to the ON state in the absence of appreciable EMG activity. Also, in this way the technician can make sure that the EEG is recorded and processed properly.

More effective EMG IF can be constructed analyzing current density in regions especially sensitive to artifacts. Jaw tension is falsely visualized by LORETA in temporal regions. Neck tension is reconstructed as if it was produced in occipital regions and forehead tension is seen in frontal regions. According to our experience, muscular artifacts generated by

the same muscular groups are consistently visualized in specific locations. One could base the filter on high-frequency information derived in these regions and use voltage analysis as well.

2.5 The Physiological Signal (PS)

Having discussed the issue of artifacts and how we can manage them, we now turn to the physiological signal itself (PS). The choice of the PS is of primary importance for the efficacy of the neurofeedback training. In this section we review the most commonly used PS as found in the literature. In the next we introduce the PS we used, a mapping function never used before called the Φ^1 function.

The most common way to obtain real-time frequency specific information has been discussed in section 1.4 as applied to LORETA data. We illustrated the frequency-specific time domain LORETA (FTD LORETA) analysis. The EEG at all available cranial scalp electrodes is filtered for the band-pass of interest and the response of the filter constitutes the input for the time domain LORETA computations (Φ vector in equation 1.1.2). Current density in the ROI is averaged to form the PS. In scalp neurofeedback, more simply, the absolute magnitude of the filter response at the active electrode/s is computed to constitute the PS. Taken as they are these measurements are an estimation of the magnitude (square root of the power) for the band-pass of interest. Let us denote by "α" this quantity. It is well known that α naturally oscillates as the total energy of the signal oscillates, that is, even if the energy of the α band-pass decreases as compared to the total energy, in absolute terms α may increase. For this reason *normalized* measurements are preferable. Dividing α by the magnitude obtained on the unfiltered EEG provides a measure of the relative magnitude. Considering the ratio between the magnitude in two bands, say α/β, also normalizes the signal since the α/β ratio is the same if absolute or relative measurements for α and β are used. Ratio feedback is widespread. For example the protocol for the treatment of the Attention Deficit Disorder consists in suppressing the Theta (4-7 Hz) - Beta (16-20 Hz) ratio at the electrode placed on or close to the vertex (Lubar, 1991). Normalization can be achieved otherwise by considering two locations simultaneously, say $\alpha 1$ and $\alpha 2$, and extracting a measurement of their difference such as $(\alpha 1-\alpha 2)/(\alpha 1+\alpha 2)$. For example, referencing the frontal electrodes F3 (left) and F4 (right) to the vertex and defining $\alpha 1$ as the 8-12 Hz

magnitude recorded at F3 and α2 as the 8-12 Hz magnitude recorded at F4, such a quantity provides a measure of frontal brain asymmetry and its suppression is used in the treatment of depression (Rosenfeld, 2000). Again, it can be easily verified that (α1-α2)/(α1+α2) results in the same quantity regardless if α1 and α2 are evaluated in absolute or in relative terms.

In our experimental studies we were interested in suppressing low alpha activity (α: 8-10 Hz) and enhancing low beta activity (β: 16-20 Hz) in the anterior cingulate cognitive division. Let us introduce some notation so to ease the discourse. Such a protocol (enhance low beta (β)/suppress low Alpha(α)) will be indicated as α-|β+. A natural choice for a PS using the α-|β+ protocol would be the α/β ratio, as seen in the previous paragraph. Recently Rossiter (2003) discussed the advantage of the ratio feedback. The physiology and morphology of the α and β EEG signal is different. For instance, while alpha activity tends to occur in more or less prolonged burst of synchronized high amplitude, the beta activity tends to occur in bursts or spindles of desynchronized low amplitude. Changes over short time periods in these two bands will depend on all these factors. The major limitation of normalized measurements is that they do not have known expected mean, nor the expected mean in different individuals is supposed to be the same. For example, consider the ratio measurement. Its expected value depends on the DC level of the power in the two frequency band-passes. These DC levels are not the same in different individuals We introduce the Φ^1 function as an attempt to devise a dimensionless PS.

As a final remark we notice that if *frequency normalization* has been considered in the literature, *spatial normalization* did not receive much attention so far. In scalp neurofeedback spatial normalization would be achieved, for instance, dividing the absolute magnitude at the active electrode by the sum of the absolute magnitude at all electrodes. The equivalent for tomographic neurofeedback would be to divide the magnitude of the current density (current density module, see 1.3.1) at each voxel by the sum across all voxels before to compute the average in the ROI. While frequency normalized data indicates how much the magnitude increases or decreases as compared to the magnitude in other frequency bands, spatial normalized data indicates how much the magnitude increase or decrease as compared to other brain locations. In PET and fMRI data analysis spatial normalization is routinely performed (Petersson et *al*, 1999). Spatial normalization requires more intensive real-time computations. In scalp neurofeedback, the magnitude at many scalp locations has to be evaluated. In Tomographic neurofeedback current density has be estimated in all the volume.

2.6 The Φ^1 Function

We now will discuss the PS we actually employ in our experimental studies. We employed a α-|β+ protocol, with alpha in the 8 to 10 Hz range and beta in the 16 to 20 Hz range. The power in these two band-passes is continuously extracted in short time intervals (< 500msec). A natural physiological signal for this protocol, as seen in the previous section, is the α/β ratio. Instead of using the ratio of the two power measurements let us consider the *fractional changes* (Δ) at each instant time *t*:

$$\Delta_\alpha = (\alpha_t - \alpha_{t-1}) / \alpha_{t-1} \qquad (2.6.1)$$

$$\Delta_\beta = (\beta_t - \beta_{t-1}) / \beta_{t-1} \qquad (2.6.2)$$

If multiplied by 100, Δα and Δβ are the percent changes in the alpha and beta power respectively at instant time *t* as compared to instant time *t-1*. The ratio Δα / Δβ is no longer a natural measure of the overall changes because the quantity Δα and Δβ are signed, thus the ratio is meaningless. The Φ^1 function is one of the meaningful physiological signals that can be extracted when we deal with changes instead of raw measurements. Figure 3 shows how the changes in the two band-passes can be plotted in a trigonometric space. Any measurement extracted can be represented as a point in the space with coordinates [Δα, Δβ]. An example of the plot is represented in Figure 3. The point corresponds to around 50% increases in both alpha and beta power, hence it is found in the first quadrant. Two relevant parameters summerize the outcome exhaustively. These are the *distance* of the point from the origin, which is indicated by a segment labeled *r* in Figure 3, and the *angle* of the segment, indicated by θ in Figure 3. *r* and θ are the *polar coordinates* of the point with Cartesian coordinates [Δα, Δβ]. They are defined as it follows:

$$r = \sqrt{(\Delta\beta^2 + \Delta\alpha^2)} \qquad (2.6.3)$$

$$\theta = tan^{-1}(\Delta\beta / \Delta\alpha) \qquad (2.6.4)$$

θ contains information about the *direction* of the change. r contains information about the *strength* of the change. The symbol tan^{-1} means arctangent. Any possible outcome of measurements will fall in the plane and is conveniently expressed by its polar coordinates (θ, r).

Next, we need to set up a function that varies according to our protocol. For instance, for our α-|β+ protocol we wish to use a function that increases proportionally to Δβ and inversely proportionally to Δα. More specifically, the function needs to take into account eight possible outcomes as depicted in Figure 4. In Figure 4 the trigonometric space is divided in the eight octants. They are labeled and counterclockwise ordered with roman numbers (I, II, III, IV, V, VI, VII, VIII). Octants are also labeled according to how desirable or undesirable the outcome is. A "+" means moderately desirable, while a "–" means moderately undesirable. The symbol "++" means extremely desirable and "–" means extremely undesirable. Any point in the space will fall in one of the octants. If the point falls in octant I, both α and β power increases, however α increases fractionally more then β. The outcome is undesirable (-). In octant II both α and β power increases, however α increases fractionally less then β. The outcome is desirable (+). In octant III and IV α power decreases while β power increases. This is the most desirable outcome for the α-|β+ protocol, thus the outcome is extremely desirable (++). In octant V both α and β power decreases, however α decreases fractionally less then β. The outcome is desirable (+). In octant VI both α and β power decreases, however α increases fractionally less then β. The outcome is undesirable (-). Finally, in octant VII and VIII α power increases while β power decreases. This is the most undesirable outcome for the α-|β+ protocol, thus the outcome is extremely undesirable (--). We need to set up a function that converts the angle θ into a meaningful information about the direction of the outcome. The function will vary according to the desirability/undesirability of the outcome acquiring a positive sign for desirable outcomes and a negative sign for undesirable outcomes. A sine function may adequately serve the purpose. For our protocol this is given by $sin\ \theta$-45°. Here 45° represents the angular coordinate of the sine function. The sine function starts at 45°, reaches its maximum (+1.0) at 135°, returns back to zero at 225°, reaches its minimum (-1.0) at 315°, and finally returns to zero back at 45°. In Figure 4 it can be seen that $sin\ \theta$-45° varies according to the desirability/undesirability of the outcome according to the α-|β+ protocol.

More in general, any protocol involving two band-passes can be arranged changing the angular coordinate of the sine function. In general, the sine function will be:

$Sin\ (\theta-\gamma)$ (2.6.5)

Where θ is given by (2.6.4) and γ is the angular coordinate (constant). Here below is an exhaustive list of adequate sine functions for any combination of enhancing/suppressing protocol involving two band-passes, α and β, where $\Delta\alpha$ is plotted on the abscissa and $\Delta\beta$ on the ordinate:

α-|β+ protocol:	$sin\ (\theta-45°)$
α-|β- protocol	$sin\ (\theta-135°)$
α+|β- protocol	$sin\ (\theta-225°)$
α+|β+ protocol	$sin\ (\theta-315°)$

(2.6.5) converts the direction information (2.6.4) into a meaningful quantity. So far we have been concerned about the direction information only. The strength of the outcome (2.6.3) also plays an important role. For instance, compare a 200% increase in β accompanied by a 200% decrease in alpha with a 100% increase in β accompanied by a 100% decrease in alpha. Such two outcomes have the same angle θ but different strength r. Indeed the former is more desirable than the latter, since it indicates a stronger change in the desired direction. While we wish to set up a function that accounts adequately for the strength of the outcome, we also wish such a function to have bounded dynamical range. The following negative exponential function may serve the purpose:

$(1-e^{-r})$ (2.6.6)

(2.6.6) assumes a zero value when the strength r (2.6.3) is zero and asymptotically reaches 1.0 as the strength r goes to infinity.

The Φ^1 function is defined multiplying (2.6.5) by (2.6.6):

$\Phi^1 = (1-e^{-r})\ Sin\ (\theta-\gamma)$ (2.6.7)

Φ^1 is bounded between –0.1 and 1.0. Since it has two parameters, r and θ, the function unfolds in three dimensions. Figure 5 shows mesh plots of the function Φ^1 in the original $\Delta\alpha$ and

$\Delta\beta$ coordinates. Both axes were restricted to ± 7.0, the equivalent of a 700% change in alpha and beta. In Figure 5 the x-axes (dotted line) is $\Delta\alpha$, while the y-axes (dotted line) is $\Delta\beta$. The z-axes (solid line) is the value of Φ^1. The function is seen from three different angles. All pictures were obtained rotating the plot around the z-axes while keeping the other two axes constant. Yellow points represent positive values (max=1), blue points represent negative values (min=-1.0). Points with value close to 0 are represented in light gray. Φ^1 reaches its maximum faster for higher values of the sine of the angle. The peaks on the z-axes (where the function bends the most) are observed when Sin (θ-γ) is either 1.0 or −1.0. Those are the most desirable and the most undesirable outcomes respectively. For values of Sin (θ-γ) close to zero (at the outer borders of the mesh), the function riches its maximum slower, meaning that an extreme high value of r is necessary to result in a high value of Φ^1.

The dimensionless property of (2.6.7) assumes that the brain is a homeostatic system with fractional changes comparable across individuals. If so, the expected value of Φ^1 should be zero. In other words, assuming that changes in the two band-passes of interest cannot happen indefinitely in the positive (increase in power) or in the negative (decrease in power) direction, and assuming that changes in one direction will be similarly compensated by changes in the opposite direction so to keep a sort of symmetric homeostasis, then over a sufficiently long period of time the fluctuations of Φ^1 will cancel out leading a sample mean of zero. Our empirical observation is that Φ^1 for alpha (8-10 Hz) and beta (16-20 Hz), as averaged every 250 msec, oscillates more or less randomly around zero with sample means close but not equal to zero because the empirical distribution of the Φ^1 function is not exactly symmetric. This suggests that positive and negative changes are subjected to different physiological dynamics.

2.7 Types of Learning Curves

In general, aim of neurofeedback is to enable the individual to acquire sufficient control over his/her own brain electrical processes. Thanks to this control the individual can shape the activity in desired directions. The purpose is either clinical (amelioration of a pathological condition), or experimental. Neurofeedback is a *learning* process. Most individuals, but not all, are good learners of neurofeedback-driven brain activity modification. Both in a clinical and in an

experimental context it is of interest to show the progression of the learning process over time and to verify that it leads to the desired modifications. In section (2.3) we stressed the duality of the learning process involved in neurofeedback; the *self-regulation* aspect implies volitional control acquired through an act of motivation. The *operant conditioning* aspect implies the increased frequency of a brain state obtained by reinforcement. In this section we analyze the types of learning that can be achieved and tested by means of neurofeedback. In the next we will illustrate a suitable statistical analysis framework for these types of learning processes. First, let us introduce some terms to ease the discussion. As in all learning processes, neurofeedback-driven learning appears over time. The time elapsed from the moment the subject enters the neurofeedback setting to the moment he/she leaves is called a *session*. The actual time spent continuously in neurofeedback is called a *trial*. There can be many trials within a session. For instance, the subject may undertake four trials of 10 minutes each within each session. The usual total training time for each session is 20 to 40 minutes. Sessions are usually spaced two-three days apart. The number of sessions required to learn varies across individuals. In general 20 to 40 sessions are required to achieve substantial modifications. The first signs of learning may be observed after a few sessions. However, it all depends on what we exactly mean by *learning*.

In the literature neurofeedback learning has been defined inconsistently. The learning process can be classified according to the *extent of this effect* (temporary versus permanent), and the *nature of its action* (controlled versus uncontrolled). Based on this conceptualization we individuate not less than four types of learning in neurofeedback:

1) Long Term learning. (LTL) This is the most difficult to obtain, but it is the only one of clinical relevance because it provides evidence of *permanent* changes in brain electrodynamics. LTL occurs whether modifications in some brain activity are observed at times far apart from the sessions. To test the LTL hypothesis one has to collect EEG recordings *before* each session (or at any other times far apart from the sessions, but not soon after because of "rebound" effects), and show trends in the parameter of interest (e.g. the average alpha/beta power ratio) as extracted in these recordings. If trends in the desired direction appear we have evidence that brain electrodynamics underwent stable changes. Follow up recordings after the training is completed are needed in order to claim that changes do not revert back to pre-training values. LTL has been shown, for example, by Lubar & Shouse (1976).

2) Within Sessions Learning (WSL). This is easier to obtain as compared to LTL but is of little clinical utility. The parameters of interests (e.g. the average alpha/beta power ratio) are extracted *during* each session. As for LTL, the learning appears over sessions. The subject is able to change the brain activity while neurofeedback occurs, but there is no evidence that the changes last after the session is ended. In other words, the learning is temporary.

3) Within Trials Learning (WTL). Several trials may be run in each session. It may be of interest to test if the subject learns across trials. In this case the parameter of interest is extracted at each trial and for each trial it is averaged across sessions. Learning here appears over trials and provides evidence of the fact that the individual was able to determine modification of brain electrodynamics while exercising. A similar result is obtained by averaging the performance over time across each session. Being temporary as the WLS, this kind of learning is of no clinical utility. It has been shown, for example by Vernon et *al.* (2003).

4) Volitionally Controlled Learning. (VCL) None of the above types of learning uncovers the nature of its action. In fact, all these three types of learning may appear outside any volitional control of the process as exercised by the subject. To conclude that modifications occurs because of the individual's will, we need to ask the subjects to deliberately produce the desired modification (experimental trials) and to deliberately abstain from producing it, or to produce the opposite of the desired modification (control trials), Comparing experimental and controls trials we can test the hypothesis that the subject acquired control of his/her brain electrodynamics and that he/she is successful in determining the desired modification at will. Although such a control cannot be demonstrated to be permanent, RTL has important implications for our understanding of the neurofeedback process as a whole and for its clinical applications. Note that the presence or absence of VCL is independent from the presence or absence of the other three types of learning mentioned before; these types of learning may or may not appear regardless of the fact that they are volitionally controlled or not.

2.8 Statistics for Learning Curves and Randomized Trials

Each of the four types of learning analyzed in the previous section needs dedicated data collection. However statistical analysis for the first three types of learning is identical and will be treated first. The plot of the "performance" (electrophysiological parameter) over time (session) for each individual makes a train of dots as in a scatter plot. Connecting the dots results in a graph known as *learning curve*. Typically, learning is indicated by an upward or downward trend of the curve. For example, for a α-|β+ protocol, the electrophysiological parameter could be the α/β power ratio and learning is indicated by a significant downward trend. Since the trend is not required to be linear, but only monotonic, Spearmann's correlation seems a suitable statistic summarizing the evidence of the trend hypothesis. However, trends in the parameter of interest may be the result of intervening variables such as extra-cranial artifact. For instance, in our α-|β+ protocol the α/β power ratio may decrease because of a decreasing EMG activity erroneously interpreted as β. Therefore the influence of intervening variables has to be removed before to run the analysis. Unlike Pearson's correlation, Spearmann's correlation does not allow a straightforward approach for computing partial correlations. Furthermore, correlation analysis does not allow hypothesis testing on the interaction of several parameters. A more suitable statistical framework for the analysis of learning curves is a linear regression model with intervening variables entered in the model as covariates. Higher order models (quadratic, cubic, etc.) can be used if the learning curve does not appear to be linear. For our regression analysis we relied on exact randomization ordinary least square (OLS) linear regression model (Manly, 1997) as computed from the BLOSSOM statistical package (Cade & Richards, 1999). The test procedure implemented in the program is the randomization equivalent of an analysis of covariance (ANCOVA) and is explained in details by Kennedy & Cade (1996) and by Anderson & Legendre (1999). This statistical analysis suits the types of learning 1), 2), and 3) analyzed in the above section, and with a slight modification, it suits type 4) as well.

VCL (see previous section) implies the use of randomized trials. In a session we ask the subjects to deliberately produce the desired modification for a certain number of (experimental) trials and to deliberately abstain from producing it or to produce the opposite of the desired modification for a certain number of (control) trials. In our experiment we used eight 3-minutes trials, of which four of the "1" kind (deliberately produce the desired modification) and four of

the "0" kind (deliberately abstain from producing the desired modification). For all trials we evaluate the parameter of interest. If the order of experimental and control trials is truly chosen at random, then a randomization test on the difference of the means (Edgington, 1995) in the two conditions (experimental versus control) will provide an exact p-value for the experiment. However, again, we could not control for intervening variables, nor could we study the interaction of several parameters. A better solution is provided by an exact randomization ordinary least square (OLS) linear regression model as just seen. At each trial the performance is extracted and constitute the major dependent variable. Extra-cranial artifacts and other intervening variables enter the model as covariates. The only difference is that the independent variable is no longer the sessions (1, 2, 3....), but a dichotic dummy variable indicating the condition (experimental versus control).

2.9 The Combination of p-Values

Neurofeedbaack experiments are always a collection of single-case experiment. The learning process is definitely something peculiar to each individual. For no reason we should expect the learning curve of an individual to be congruent with the learning curve of another individual. This is one of those experimental situations in which average group analysis is meaningless. Nevertheless, to obtain external validity (generalization to population) we wish to provide evidence of learning on a sample of individuals considered as a single entity and not as a mere collection of entities. Instead of averaging data of all individuals we can run single-case statistical tests and then combine the p-value obtained across individuals. A combination of "n" p-values is a p-value itself. It is the probability to obtain "n" p-values as small as those observed, given that the complete null hypothesis is true. The concept is similar to multivariate tests, where a unique p-value is derived for all variables. The combined p-value provides evidence that the effect is tested separately for each case, and is indeed consistent across all cases. Note that for the combined p-value to be the significant it is not necessary that all individual p-values are significant. As an extreme example, fifty individual p-values equal 0.2 would result in a significant combined p-value because the probability to observe fifty p-values as small as 0.2 in fifty individuals, given the null hypothesis is true for all of them, is indeed very low. The most important advantage of this approach is that it does not require that the experimental conditions

be identical for all subjects, nor that the learning process is the same in different individuals. For example, the approach remains valid if the number of sessions is different across individuals. Also, the individual differences generating learning curves of different shape does not constitute a nuisance source of variation. Finally, the sample size is not a concern in p-value combination. The combination of very few p-values is as legitimate and valid as it is the combination of many p-values. The only assumption of (parametric) p-value combination is that the p-value be all pair-wise independent. Since in neurofeedback we always derive p-values for each individual separately, and since individuals are truly independent statistical units, the approach is always valid.

They exists several methods to combine p-values. In our experimental studies we used systematically two of them, namely the *additive* combining function of Edgington (1995) and the well-known multiplicative combining function based on the sum of the logarithm of p-values, due to the father of modern statistics, Sir Roland Fisher (e.g., Pesarin, 2001). We chose to use both these two functions because they display quite a different sensitivity for extreme configurations of p-values (Edgington, 1995). In particular, the multiplicative combining function is more sensitive to configurations where there is one or more extremely small p-value. The additive combining function is more sensitive when the p-values are all similar to each other. Hereafter we will refer to the additive combining function with the symbol P^{+}, and to the multiplicative combining function with the symbol $P^{\times}$.

Chapter 3

Experimental Studies

3.1 Introduction

The role of experimentation is essential in the scientific investigation of neurofeedback-driven learning. The fundamental aim of this dissertation is to show that learning with LORETA neurofeedback is achievable. In this respect, an experimental result is the only convincing evidence. In fact previous results obtained in scalp neurofeedback are not readily translated into LORETA neurofeedback. Once LORETA neurofeedback learning is demonstrated, which implies a sufficient body of evidences, research could take several directions exploring the advantages offered by the method. In this chapter we present the results of one experimental study conducted at the Brain Research and Neurophysiology Laboratory (Director: Dr. Lubar) at the University of Tennessee. The study is only a first step toward an experimental validation of the method. The first experiment was conducted during the academic fall 2002 semester. It was a combination of three intensive single-subject time-series experiments carried out over a period of three months. Participants underwent several sessions of LORETA neurofeedback in order to enhance low beta (16-20 Hz) and suppress low alpha (8-10 Hz) current density power in the anterior cingulate cognitive division (ACcd). Electrophysiological and psychometric tests were continuously administered during the experiments. Experimenters were undergraduate students at the Department of Psychology of the University of Tennessee taking classes for research practicum. They were trained, instructed, coordinated and constantly supervised by the author and their Professor, Dr. Joel Lubar.

We collected several gigabytes of data suitable for testing complex hypotheses related to successful modification of the electrical activity in the ACcd by means of LORETA neurofeedback. The region of interest (ROI=ACcd) is depicted in Figure 6 using the LORETA-Key (Pascual-Marqui, 1995) implementation (see section 2.6). The region includes 38 voxels of 7x7x7 mm. size, for a total extent of 13.034 cm^3. With other functional neuroimaging techniques

such as PET and fMRI, the ACcd has been consistently shown to be actively involved in attention processes (Bush et *al*, 1999; Devinsky, Morrell, & Vogt, 1995).

The choice of the band-passes was dictated by the EEG literature. Converging evidences point to the role of frontal alpha and beta power in attention. A common pattern of abnormality in the electrophysiology of individuals affected by attention deficit disorder with (ADHD) or without hyperactivity (ADD) includes excessive low alpha power and weak low beta power (Barry, Clarke, & Johnstone, 2003; see also Barry, Johnstone, & Clark, 2003). Those individuals have a very short attention span and poor mental focusing capabilities. On the other hand alpha activity is known to decrease during cognitive functions (Nunez et *al.*, 2001) and to be inversely related to metabolism (Leuchter et *al.*, 1999). For over thirty years Lubar (1991) employed 16-20 Hz power enhancement protocols (in mid-frontal locations Fz, Cz or Pz) to enhance attention in individuals suffering from ADD/ADHD. Putting together these pieces of information we decided to suppress low alpha (α) and enhance low beta (β) power with the aim to facilitate attention processes.

In the next section we illustrate the equipment (hardware and software) we built in order to carry out experimentation. Then, we report the methods and results of the set of experiments. The chapter ends with concluding remarks.

3.2 Equipment

For experimental purposes two computer applications working in the Windows (Microsoft, Inc) OS were written. The first application, hereafter referred to as RTL (Real-time LORETA) was written in the C language by our collaborator David Joffe, an engineer working for Lexicor Medical Technology, Inc. in Boulder, Colorado. The second one, hereafter referred to as LNF (LORETA NeuroFeedback) was written in Delphi 5 (Borland, Inc.) by the author of this dissertation. David Joffe designed many years ago the EEG acquisition device Neurosearch-24 (Lexicor Medical Technology, Inc.). RTL is synchronized to the Neurosearch-24 to extract EEG and compute LORETA inverse solutions in real-time. Also, in real time RTL sends out via serial port (null-modem cable) relevant information to another computer. LNF inputs this information

via serial-port, processes it, delivers the appropriate visual and/or auditory feedback to the subject, and writes the data for within-sessions performance analysis. The two programs work together and complement each other. RTL and LNR run on two distinct but connected (via serial port) computers so to have access separately to two computer monitors, one for the experimenter and one for the participant (Figure 7).

The *Neurosearch-24* EEG acquisition machine (http://www.lexicor.net) has 24 dedicated amplifiers. EEG data for the 19 standard 10-20 locations was acquired in the 0.5 to 64 Hz band-pass (with a 60 Hz notch filter for power supply noise), digitized with a 12 bit A/D (analog to digital) converter and sampled at 256 samples per seconds. A Pentium I (Intel, Inc.) PC computer working in Windows 98 (Microsoft, Inc.) served as storage of the digitized data and as the first monitor for RTL display.

RTL manages and operates the Neurosearch-24. The program continuously extrapolates and displays on a computer screen the stream of EEG. This screen is observed by the technician so that he/she can monitor the EEG, check the behavior of the inhibit filters for the extra-cranial artifacts (section 2.4), and make sure that other sources of artifacts do not appear (e.g., lost contact of an electrode). Since LORETA inverse solution is a weighted sum of scalp potentials it is necessary to ensure that the signal at all electrodes is clean. At the same time the RTL filters the EEG in the band-passes of interest and in the 35-55 Hz range for the EMG inhibit filter (IF, see section2.4). The average current density in the region of interest (ROI) is computed via equation (1.1.2) for all these band-passes. In addition RTL computes the maximum absolute voltage across frontal electrodes for the EOG IF (2.4). All this information is sent via serial-port to another computer where LNF is running. In our experiments the output of RTL was always 4 real-time channels, in the order, α, β, EMG, and EOG. α and β are the average current density in the ROI as computed on the low alpha (8-10 Hz) and low beta (16-20 Hz) filtered EEG respectively. EMG refers to the average current density in the ROI as computed on the 35-55 Hz filtered EEG. EOG refers to the maximum absolute voltage across frontal electrodes FP1, FP2, F7, F8, F4, F3 (see section 2.4).

LNF runs on the receiving computer. It inputs in real time the four channels and administers the neurofeedback trials. From the time series of α and β, the Φ^1 function (2.6.7) is computed. This is the physiological signal (PS) with which a continuous feedback signal (CFS,

see section 2.1) co-varies. LNF supports both auditory and visual CFS. The *visual* CFS has the form of a moving scatter plot where each value of Φ^1 is represented by a squared dot. Figure 8 shows a snapshot of the subjects' screen during LORETA neurofeedback. The horizontal line in the middle of the moving scatter plot corresponds to a zero value. Dots above the line indicate positive values (desirable changes), while dots below the line indicate negative values (undesirable changes). The *auditory* CFS implemented by LNF is a short (100 ms) tone whose pitch increases proportionally to Φ^1. The range [-1.0, 1.0] of the Φ^1 function is divided into 21 equal intervals. To each interval, from the lower to the upper, it corresponds a pitch increasing as the 21 notes comprising three octaves of the C major scale. In all our experiments the Φ^1 function was updated every 250 ms.. With such a short interval the feedback received is almost continuous, hence the name "continuous feedback signal".

The EMG and EOG channel are used to manage the Inhibit Filters. Anytime the EMG or EOG signal exceeds its threshold (see section 2.4), LNF sets the corresponding inhibit filters on and interrupt the CFS. The CFS resumes after 1 second during which the filter has been off continuously. The status of the Inhibit filters are communicated to the subject by means of flashing lights on the screen (Figure 8).

In section (2.3) we discussed the different conception behind a self-regulation and an operant conditioning paradigm. Self-regulation is better achieved using a CFS (Hardt and Kamiya, 1976), while operant conditioning requires the use of a discrete reinforcement (Sterman, 1973). We will refer to the latter as discrete feedback signal (DFS). LNF supports both auditory and visual DFS. The *visual* DFS has the form of a large flashing light on the screen (Figure 8). The color of the flashing light may be chosen by the subject so to be as pleasing as possible to him/her. The *auditory* DFS is a fast sequence of tones well discernible from the auditory CFS. The DFS (light flash or sequence of tones) is released as soon as the reinforcement conditions are matched. In all our experimental studies the conditions were *the same.*

1. the Φ^1 function is above 0.1 and

2. the Φ^1 function was above 0.1 at the previous instant time (250 ms. before)

The Φ^1 function incessantly oscillates between positive and negative values. In fact factorial changes in α and β cannot proceed indefinitely in the same direction. Note that consecutive points with the same sign using the Φ^1 function as PS have a peculiar interpretation. For instance, suppose two consecutive value of Φ^1 equal 0.3. The first value indicates a quantifiable change, say "c", of α and β in the desired direction. The second indicates a *further* change of "c" magnitude in the same direction. We see that the observable number of consecutive points with the same sign has to be finite; sooner or later Φ^1 will switch sign in order to compensate for the previous changes with changes in the opposite direction.

The empirical Φ^1 function could be seen as a *random walk* with two states, positive and negative. Even after this simplification the model would require complex statistical analysis. For example this random walk could be modeled as a *recurrent* (ergodic) *Markov chain* and defined by two (transition) probabilities, p^+ and p-, which are the *probability to leave the positive state to enter the negative state* and *the probability to leave the negative state to enter the positive state* (Thomason, 2001). Such a model would assume that at each instant time the state of the chain is conditioned only to the present, and not to the past. Furthermore rhythmic (cyclical) activity and the activity of the rest of the brain are not easily taken into account. Similar arguments apply if we consider the expected number of consecutive positive and negative values in the time-series and model this random variable by means of two *Poisson distributions* with parameter (expected value) λ^+ and λ- (expected number of consecutive positive and negative points respectively).

The conditions we set for reinforcement require that the individual maintains a desirable change for at least 500 ms. The idea is to train individuals to *sustain* changes in the desired direction. The 0.1 threshold is introduced to suppress noise, that is, minimal changes of no appreciable value. In total we carried out three experiments using the protocol illustrated above. For all three individuals, the percent time spent in reinforcement state, as seen in pre-neurofeedback baselines, was around 10%. Then the λ^+ parameter has to be such that the probability to observe two or more consecutive positive values of Φ^1 is around 0.1. We can now point to an advantage of the Φ^1 function: we were able to use the same threshold and conditions for reinforcement for all individuals. Using other PS, such as those reviewed in section (2.5), a threshold attaining similar percent time spent in reinforcement state would be different for each individual.

3.3 Method

Subjects

The study was conducted from September 2002 to December 2002 at the university of Tennessee. Several undergraduate students (psychology majors) volunteered to participate in exchange of extra-credit in a psychophysiology class and for monetary compensation. Three of them were selected according to exclusion and inclusion criteria and according to their interest in the research. Potential participants or their first degree relatives had to have no history of depression, anxiety, epilepsy, eating disorder, drugs abuse, attention deficit, or any psychiatric or neurological disorders that would confound their status as non-clinical healthy college students.

History and current habits of subjects were assessed with a semi-structured interview following a questionnaire (see Appendix II). During colloquia with volunteers, we stressed the importance of obtaining truthful information from them. A standard EEG evaluation with comparison to a normative database constructed with 82 healthy undergraduate students of the University of Tennessee (Congedo & Lubar, 2003) was performed. Individuals displaying significant ($p<0.05$) deviations from the norms in terms of absolute and relative power in 13 standard band-passes at any electrode (scalp voltage power) or at any intra-cranial voxels (LORETA current density power) were excluded. All participants were required to be alcohol and medication free for 24 hours prior to sessions. After selection, the participants were carefully followed by the experimenters, who were chosen based on weekly schedule compatibility with the undergraduate students under training in the laboratory. Participants were all required to sign an informed consent (see Appendix III). All aspects of this study were approved by the University of Tennessee Human Subjects Review Board (see Appendix IV).

In selecting the participants the key factor was their interest in the research and their reliability in respecting commitments about times and days for the sessions. The three selected participants were two females and one male, aged 21, 20, and 19 respectively. They will be referred to as S I.1, S I.2, and S I.3, where the first index refers to the experimental study and the second to the subject.

Procedures

EEG recording procedures we used are standard and have been used in the Brain Research and Neuropsychologyy Laboratory for more then 10 years (e.g., Lubar & Congedo, 2003). The same procedure is applied for LORETA neurofeedback. In preparation for recording a measure of the distance between nasion and inion was used to determine the appropriate electrode cap size for recording purposes (Blom & Anneveldt, 1982; Electrocap, Inc.). The forehead was prepared as well as the ears with Nuprep, a mild abrasive gel to remove any oil from the skin. The cap was then fitted and each electrode site carefully injected with Electrogel and prepared so that impedances between each electrode site and each ear measured individually was between 3 and 5 Kohms as well as the impedance between ears themselves. The EEG was then recorded at the standard 10-20 system 19 locations (FP1, FP2, F3, F4, Fz , F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2) using the Neurosearch-24 (Lexicor Medical Technologies, Inc.). The amplification factor was 32,000. For eyes closed and eyes open baseline recordings the EEG was sampled at 128 Hz and the low and high pass filters were set at 0.5 and 32 Hz respectively. For LORETA neurofeedback sessions the EEG was sampled at 256 Hz and the low and high pass filters were set at 0.5 and 64 Hz respectively (see also section 3.2).

All baselines consisted of 3-4 minute of EEG continuously recorded. For each neurofeedback session there were six three-minutes trials. All parts of the experiment took place in a dimly illuminated and sound attenuated room at the Brain Research and Neurophysiology laboratory of the University of Tennessee. For both baselines and neurofeedback trials data was acquired using the Lexicor Neurosearch-24 device (3.2).

Baseline data was transported into the EureKa3! software (NovaTech EEG, Inc.), where it was plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movements, or EKG artifact were removed from the stream of EEG. Particular care was taken to eliminate periods of EEG containing continuous muscle artifact in temporal locations T3, T4, T5, or T6. EureKa3! also performed scalp and LORETA power analysis for baseline recordings. Data of the neurofeedback trials were provided by the LNF program. LNF reports only artifact-free data, that is, while the EMG or EOG filter is on, the program stops the writing of data output.

Protocol

As reported in section (3.1), participants underwent sessions of LORETA neurofeedback in order to enhance low beta (16-20 Hz) and suppress low alpha (8-10 Hz) current density power in the anterior cingulate cognitive division (ACcd). The ROI is depicted in Figure 6. Such a protocol is indicated in symbols as α-|β+. The rationale behind the choice of the ROI has been explained in section (3.1). In the first study RTL was instructed to compute the average current density module (1.3.1) for the EEG filtered in the α and β range and to normalize (divide) these quantities by the average current density module computed on the raw (unfiltered) EEG. This is the relative magnitude measurement we discussed in section (2.5). The Φ^1 function was extracted every 250 ms from the (relative) factorial changes for α and β according to equations (2.6.1), (2.6.2), (2.6.3), (2.6.4,) (2.6.5), (2.6.6,) and (2.6.7).

Experimental Design and Hypotheses

All three single-subject experiments have the same design and consisted of three phases plus a run of randomized trials (Figure 9). In the first phase eyes-open and eyes-closed baselines were recorded (n=10). This data was not used for subsequent analysis. In the second phase (intervention), subjects were exposed to brief neurofeedback sessions (n=12). They were allowed to experience all combination of CFS (none, auditory, visual or both auditory and visual) and DFS (none, auditory, visual or both auditory and visual), and to request other LNF settings (e.g., colors) as well. During these "intervention" sessions the experimenter and the subject worked together to find satisfactory settings. S I.1 and S I.2 experienced difficulties in running the trials with the eyes open because of their contact lenses. They underwent the training with eyes closed and used the auditory version of both the CFS and DFS. S I.3 underwent the training with eyes open. He preferred to work with the visual CFS, and both the auditory and visual DFS. Ended the "intervention"phase, all three participants performed 6 LORETA neurofeedback sessions. Each session consisted of six three-minutes trials. An eyes closed and an eyes-open baseline was collected *before* each session. Finally, during the last meeting participants undertook a randomized trials session (see section 2.8).

In section (2.3) we discussed the difference between the self-regulation and the operant-conditioning aspects of the learning process involved in neurofeedback in general. In section (2.7)

we discussed the issue in depth and we discriminated four distinct types of learning processes that can be tested using neurofeedback. These are the long term learning (LTL), the within sessions learning (WSL), the within trials learning (WTL) and the volitional controlled learning (VCL). Section (2.8) introduces the statistical procedures we can employ for each type of learning. For each subject, we tested the relevant WSL and VCL hypothesis. Since we had only six neurofeedback sessions in this study we did not test the LTL hypothesis, since this is a form of permanent learning and usually requires 20 to 40 sessions to appear. The WTL was not of interest for us.

Regarding the WSL, for each participant and for each neurofeedback session, the median of the average α power in the ROI and the median of the average β power in the ROI were extracted (n=6) as the average of the six trials. The median EMG and EOG channels as defined in section (2.4) were extracted in the same way. Learning curves of the β/α ratio over sessions were analyzed by means of a Spearmann's correlation coefficient using the EMG and EOG as partial variables. The NCSS software was used for this purpose (Hintze, 2001). Since the number of data-points we had was very small (n=6), we did not use the exact randomization ordinary least square (OLS) linear regression model (as suggested in section 2.8), since the number of parameters to be estimated for such a model was as large as the number of data points.

For the VCL hypothesis, eight 3-minute trials as explained in section (2.8) were administered. In four of them ("1") the participants tried to obtain as many reinforcements as they could. In the remaining four trials ("0"), the participants tried to obtain as few reinforcements as they could. The participants underwent the trials according to the same specifications employed during the neurofeedback sessions. The order of "1" and "0" trials was randomized shuffling eight cards, of which four reported the number "1", and four reported the number "0". The random order was established once and applied to all subjects. It was: 1, 0, 1, 0, 0, 0, 1, 1. For each participant and for each trial, the median of the average α power in the ROI and the median of the average β power in the ROI were extracted. The median EMG and EOG channels as defined in section (2.4) were also extracted. In addition, we extracted the median of the Φ^1 function and the mean percent time spent in the reinforcement state (% RS). Differences in the β/α ratio, Φ^1 function, and %RS between the "1" and "0" trials were analyzed by an exact randomization OLS linear regression model (Manly, 1997) as computed from the BLOSSOM statistical package (Cade & Richards, 1999).

In section (2.9) we presented our methodology based on the combination of p-values. For *any* hypothesis we test, the three single-subject experiments result in three p-values. The additive (P^+) and the multiplicative ($P^\times$) combining functions summarize the evidence of an overall effect. For individual p-values we set the type I error to 0.05. For combined p-values we set the type I error to 0.1, however, for claiming significance, we request that both combining functions issued a p-value less then or equal to 0.1.

Results

We tested the hypothesis that the participants attained WSL and VCL. Results for WSL are presented in Table 1. The learning curves of all the three subjects had a trend in the desired direction. The three correlation coefficients are all positive, suggesting that the β/α ratio increased over the six sessions, but none of the individual correlations was significant. The additive combination of the three p-values obtained was significant ($P^+=0.081$), however the multiplicative combination ($P^\times=0.216$) was not. Since we required both combination functions to be smaller than 0.1, we do not reject the null-hypothesis of (positive trend) WSL.

Table 2 presents the result of the VCL experiments. Table 2A reports the individual and combined p-values for the hypothesis of difference in the five dependent variables entered in the model between trials "1" and trials "0". The dependent variables were the percent time spent in reinforcement state (%RS), the β/α ratio, the Φ' function, EMG, and EOG. %RS and the β/α ratio were significant, while the Φ' function, EMG, and EOG were not. Table 2B reports the result of the equivalent of an ANCOVA where EMG and EOG are treated as covariates. Only the β/α ratio was still significant once the influence of covariates was removed. The β/α ratio increased across sessions.

The last two rows of Table 2B report the results of another similar ANCOVA where the α and the β bands are entered individually in the model. Only β was significant, suggesting that the significant increase of the β/α ratio was driven by an increase of the β current density magnitude, but not from α, EMG, or EOG. The Φ' function itself does not change. This is probably due to the homeostatic property of this function (see section 2.6).

Conclusion of the experiments

In the within-session learning (WLS), all three subjects showed a positive learning trend over sessions. The β/α ratio increased over sessions. Only one of the two combined p-values was below the alpha level, so according to our type I error the experiment does not support the hypothesis of WSL. The interpretation of these results may be as it follows: the trend showed by all our three subjects in the β/α power while undergoing neurofeedback training was in the desired direction but not significant.

In the volitional control learning (VCL), two out of three subjects individually showed volitional control. The β/α power was superior in randomized trials where the subjects tried to increase it as compared to trials where the subjects tried to decrease it. Combining the performance of all three subjects the experiment shows significant acquisition of volitional control. The effect was driven by a marked increase of β energy, while α energy did not change or was affected by artifacts. In this experiment the EMG and EOG signals did not differ significantly in the two conditions. It is worth nothing that the median value of the Φ^1 function itself did not change across sessions. This is an evidence of the fact that the Φ^1 function acts according to some sort of homeostatic process.

Conclusions

Aim of this dissertation was to implement LORETA Neurofeedback and to provide evidences about its validity as a tool for improving self-awareness of electrophysiological processes. We partially succeeded in both endeavors, however much additional research is needed. The software and hardware we constructed is of limited power and cannot be easily modify to accommodate training protocols involving complex relationship among brain regions covering a large portion of the volume. However it was adequate for the implementation of the protocol we chose for experimentation. We implemented a suppress low-Alpha (8-10 Hz.)/enhance low-Beta (16-20 Hz.) protocol in the anterior cingulate cognitive division. Further development of the hardware and software capabilities is currently being planned. They may include the real-time computation of the current density in the whole volume. With such amount of information it would be possible to device protocols based on patterns of activation in the whole neocortex instead of simply increasing/decreasing activation in a delimited fixed region. Once multiple regions of interest are supported, inter-hemispheric asymmetry protocol, and coherence protocols could be devised as well.

The experimental results we obtained were limited by the small number of sessions employed. Furthermore, by employing the Φ^{I} function we introduced a second variable in the experiment that prevents us to link these results to previous neurofeedback literature. Nevertheless we wanted to do so because we believe that a measure of brain activity that changes over time is a more convenient physiological signal as compared to raw (absolute) power. The experiment testing the hypothesis of acquired volition control provided encouraging results. On the whole, the three subjects were successful in being able to increase the β/α power ratio at will. Such an hypothesis is currently ignored in the literature on neurofeedback, but is very important in our understanding of the neurofeedback learning process. If we can show that volitional control is reachable by a significant proportion of individuals, then the efficacy of neurofeedback in a clinical setting could be related to a matter of the patient's motivation. If not, we still should inquire about the other three forms of learning achievable (see section 2.7), and establish the conditions under which they are possible. For clinical purposes the ultimate goal is to show the

long-term learning, that is, a form of changing of electrical activity that can be considered permanent and stable.

We know that learning associated with neurofeedback is achievable for most but not all individuals. Actually all we know is that experiments trying to show learning do not always succeed, and that the same is observed in the clinical practice. It is important then to understand under what circumstances the training is successful and under what circumstances it is not, and if the decisive factors for success are related to variables extraneous to the individual or to individual characteristics.

While analyzing the data from the experimental studies we realized that the Φ^I function could be considerably simplified without losing its basic properties. Arranging frequency bands in a trigonometric space makes difficult the implementation of a continuous feedback signal based on fractional changes (see section 2.6) in the case of multi-bands protocols. For example, adding one frequency band to the protocol would make the trigonometric space 3-dimensional and the Φ^I function 4-dimensional. Considering the factorial change of a ratio directly and constraining the dynamical range of this changes as we did with the implementation of equation 2.6.6., a multiple bands protocol could be obtained more simply. We could multiply the power of the bands to enhance in the nominator and multiply the power of the bands to suppress in the denominator of a ratio. The factorial changes of this ratio would have the same normalized properties of the Φ^I function. In future research we would like to follow this simpler path.

In summary, in this dissertation we showed a possible implementation of neurofeedback based on the Low-Resolution Electromagnetic Tomography (LORETA). We developed the necessary software and we carried out some preliminary experimentation. The results we obtained are encouraging but by no means conclusive. Before to proceed further in the experimentation we feel the need to revise our paradigm and to develop more powerful hardware. In the future we see the use of 3-D visors and other sophisticated apparatus for the feedback delivery. Integration of several sensory modalities seems particularly promising. In fact the more complex the feedback sensorial experience the more likely this can be associated with the electrophysiological process of interest. Henceforth speed and precision of learning may be improved considerably by means of finest technology. Furthermore, more informative feedback signals could be employed. The increase or decrease of power, typical focus of current

neurofeedback experiments and clinical applications, may provide too little information about the brain electrical activity; this limitation may make the learning process very difficult. In this study we also classified the types of learning associated with a neurofeedback training that can be measured and we introduced a new function of brain electrical activity that reflects dynamic changes along the time dimension. We do hope by means of this contribution to stimulate other research in this fascinating field.

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Appendices

Appendix I

Figures and Tables

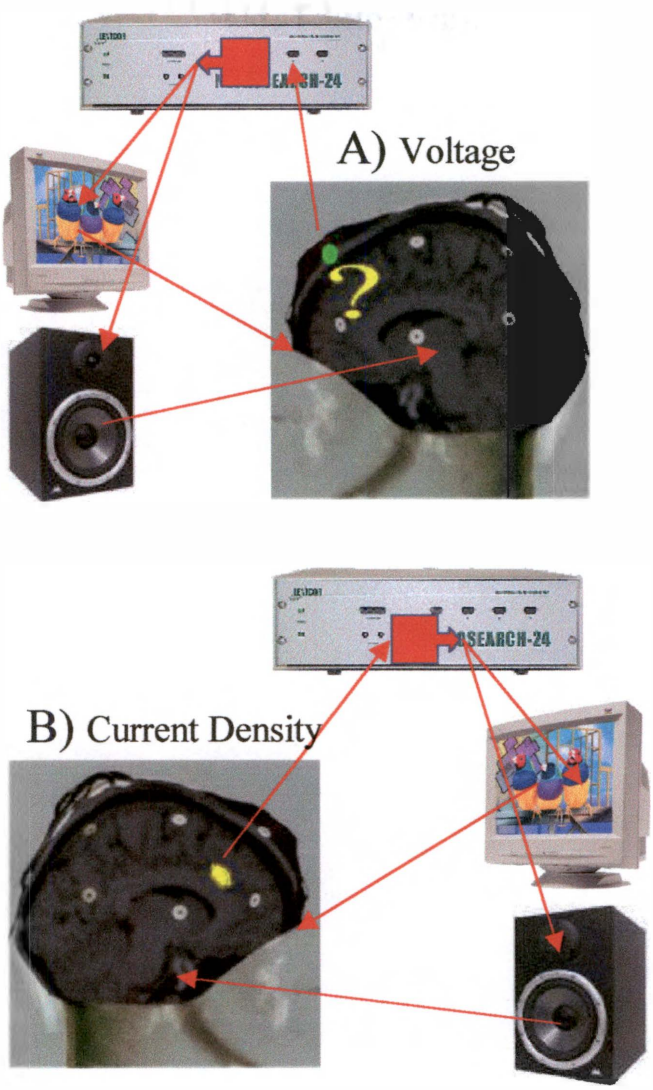


Figure 1: Schematic representation of scalp neurofeedback (A) and of tomographic neurofeedback (B). In scalp neurofeedback (A) the voltage at the active electrode (green disk) is processed by a EEG acquisition machine. A visual or auditory (or both) object co-varies with the voltage. The yellow question mark indicates the uncertainty about the actual brain region contributing to the scalp voltage signal. In tomographic neurofeedback (B) the current density of a specific region (indicated in yellow) is processed. All other steps are as in scalp neurofeedback.

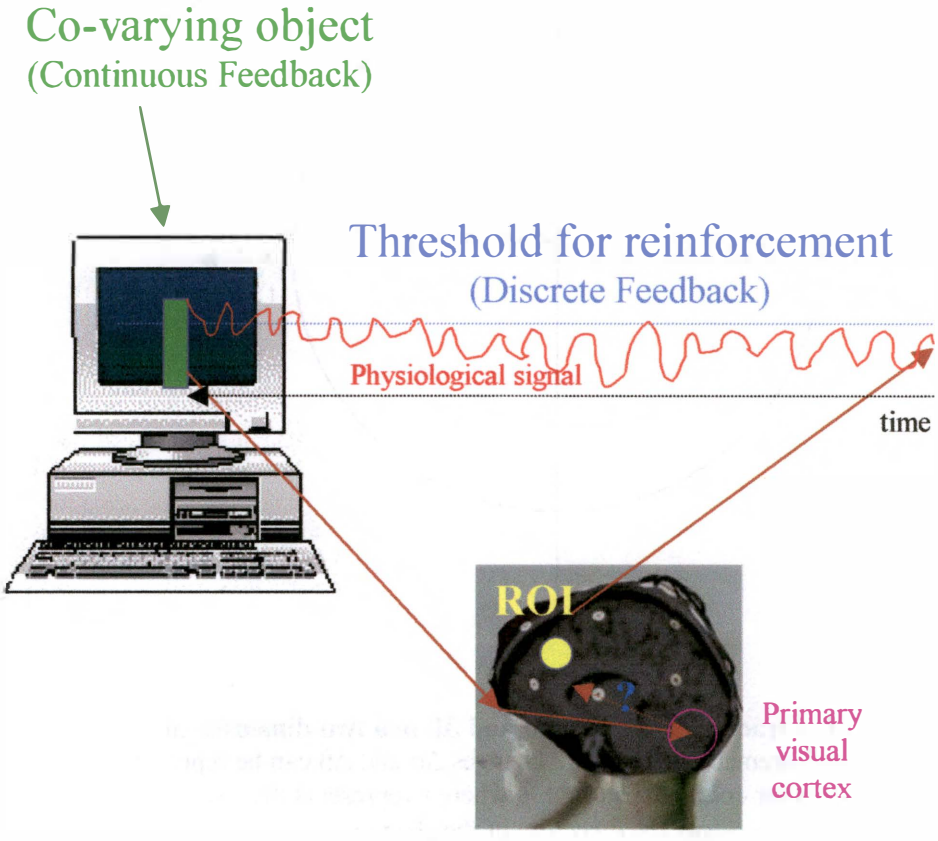


Figure 2: Another Schematic Representation of the Tomographic Neurofeedback. It shows graphically the difference between Continuous and Discrete Feedback.

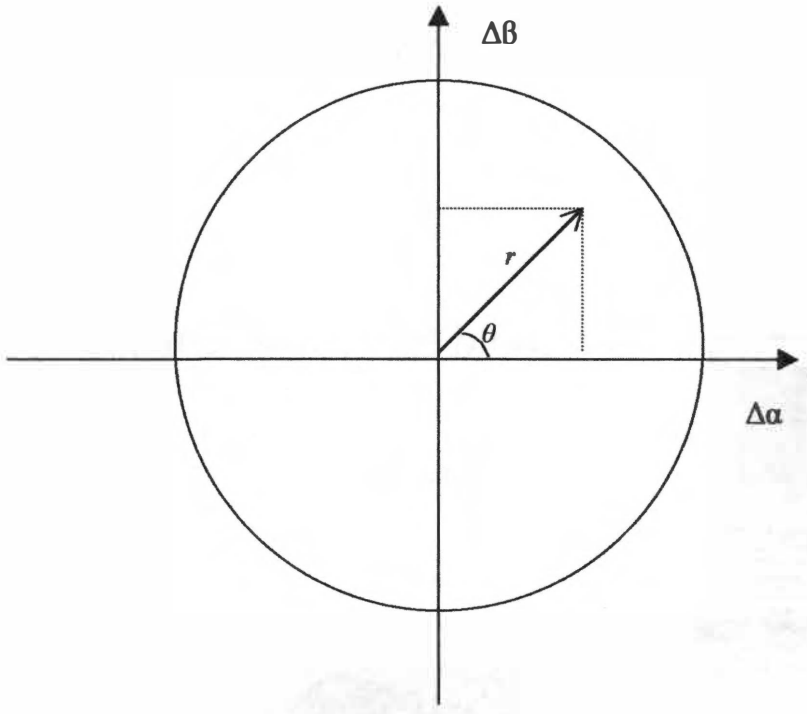


Figure 3. Plot of fractional changes Δα and Δβ in a two-dimensional space. Any measurement of fractional changes Δα and Δβ can be represented as a point with polar coordinates r and θ, where r represents the *strength* of the change and θ represents the *direction* of the change.

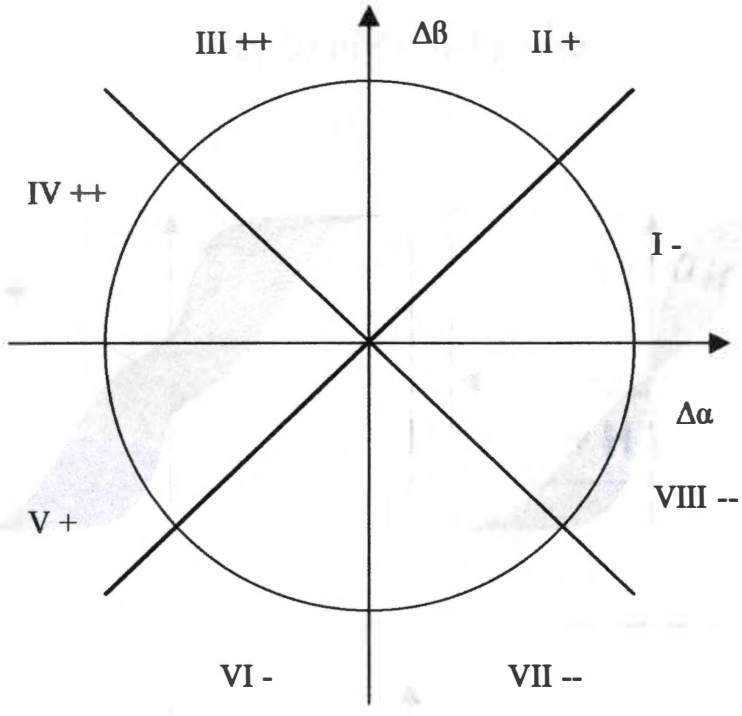


Figure 4. A trigonometric space divided in octants. The same plane as in Figure 3 is divided in octants indicated by roman letters and ordered counterclockwise. The subdivision intends to show desirable and undesirable outcome of the fractional changes $\Delta\alpha$ and $\Delta\beta$. See text for details.

$$\Phi^1 = (1-e^{-\gamma}) \text{ Sin } (\theta-\gamma)$$

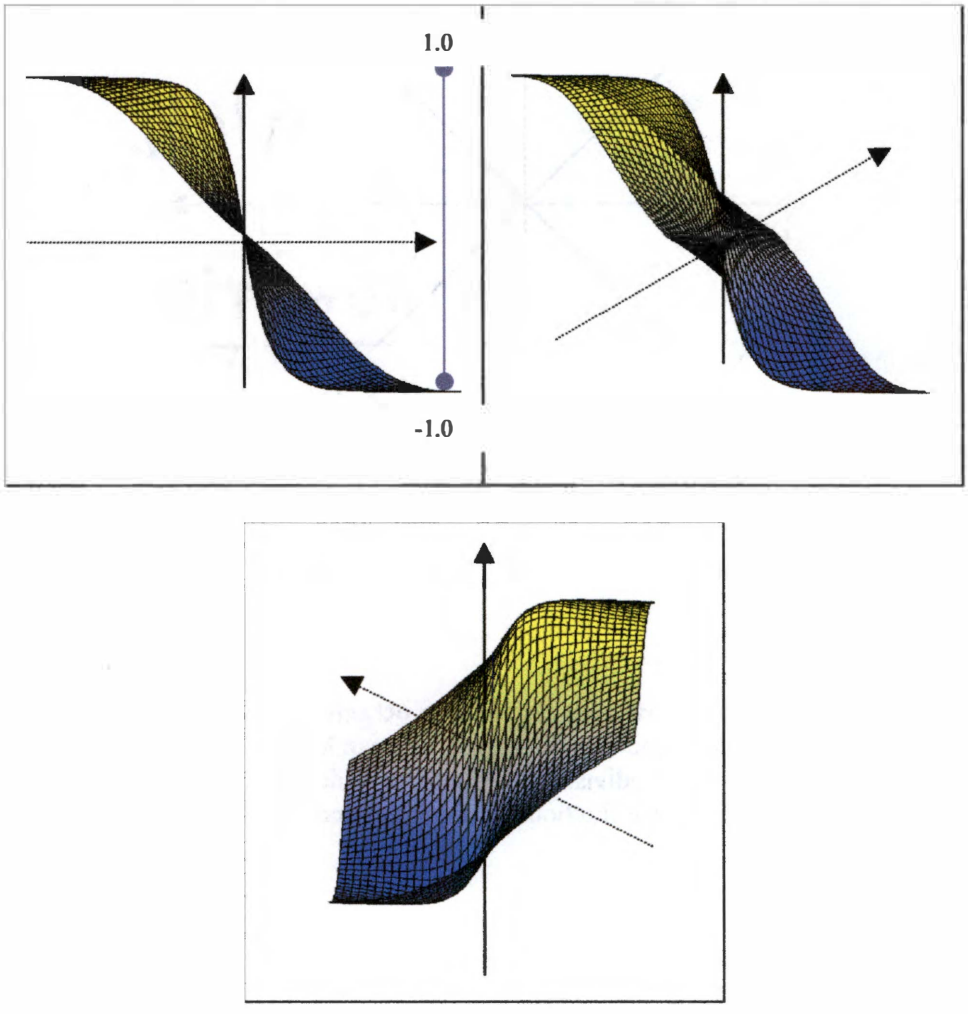
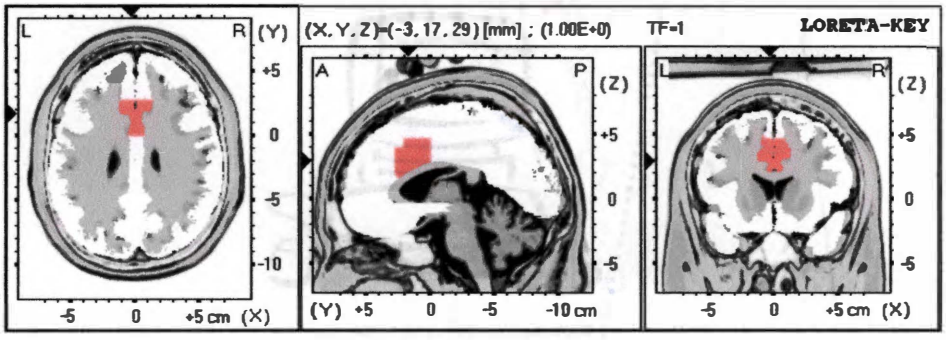


Figure 5. Mesh Plots of the Φ^1 function. x-axes (dotted axes) is $\Delta\alpha$, y-axes is $\Delta\beta$, and z-axes (solid line) is the value of Φ^1. The function is seen from three different angles. All pictures were obtained rotating the plot around the z-axes while keeping the other two axes constant. Yellow points represent positive values (max=1), blue points represent negative values (min=-1.0). Points with value close to 0 are represented in light gray. Φ^1 reach its maximum faster for higher values of the sine of the angle. See text for details.

Anterior Cingulate *Cognitive Division (ACcd);*

ROI extension = 38 voxels; Area = 13.034 cm^2



Axial view Sagittal view Coronal view

Figure 6: The Anterior Cingulate Cognitive Division (ACcd). The region of interest, the actual region of the brain trained in our experiments, is shown in red with the LORETA-Key image viewer. Axial view: left of picture is left of the brain. The slice is seen from the top of the brain. Sagittal view: left of picture is front of the brain. The slice is seen from the right of the brain. Coronal view: left of picture is left of the brain. The slice is seen from the back of the brain.

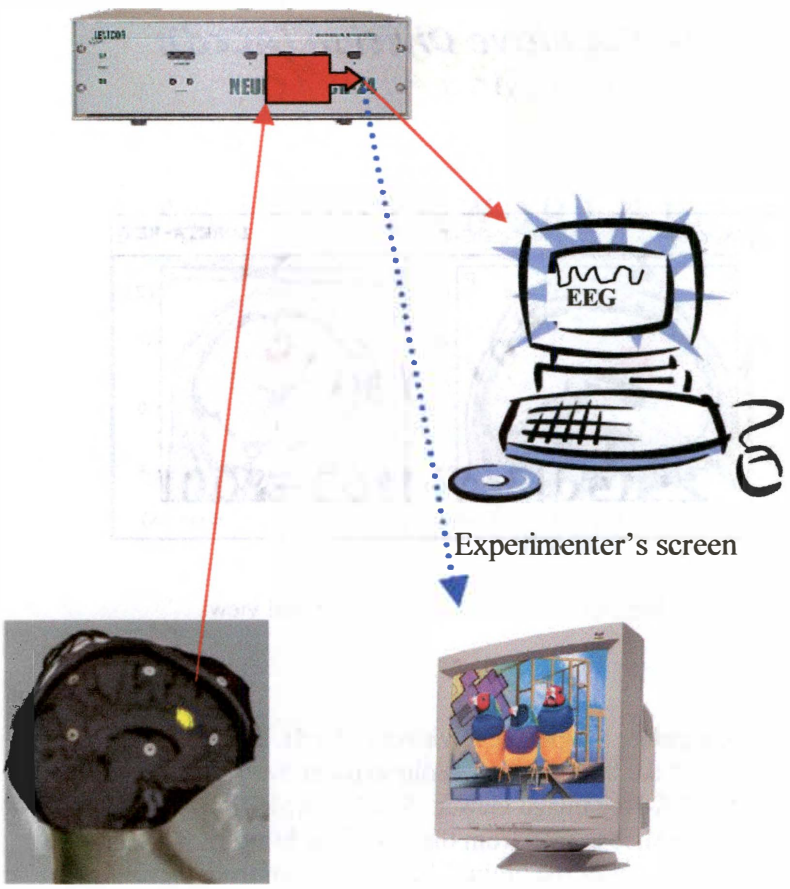


Figure 7: Schematic representation of the equipment involved in our implementation of tomographic neurofeedback. The current density of a specific region (indicated by a yellow area) is processed by a EEG acquisition machine. The real time EEG signals are displayed to the experimenter on a computer screen. Meanwhile, data from the region of interest is sent via serial port (blue dotted arrow) to another computer, which provides the feedback to the participant.

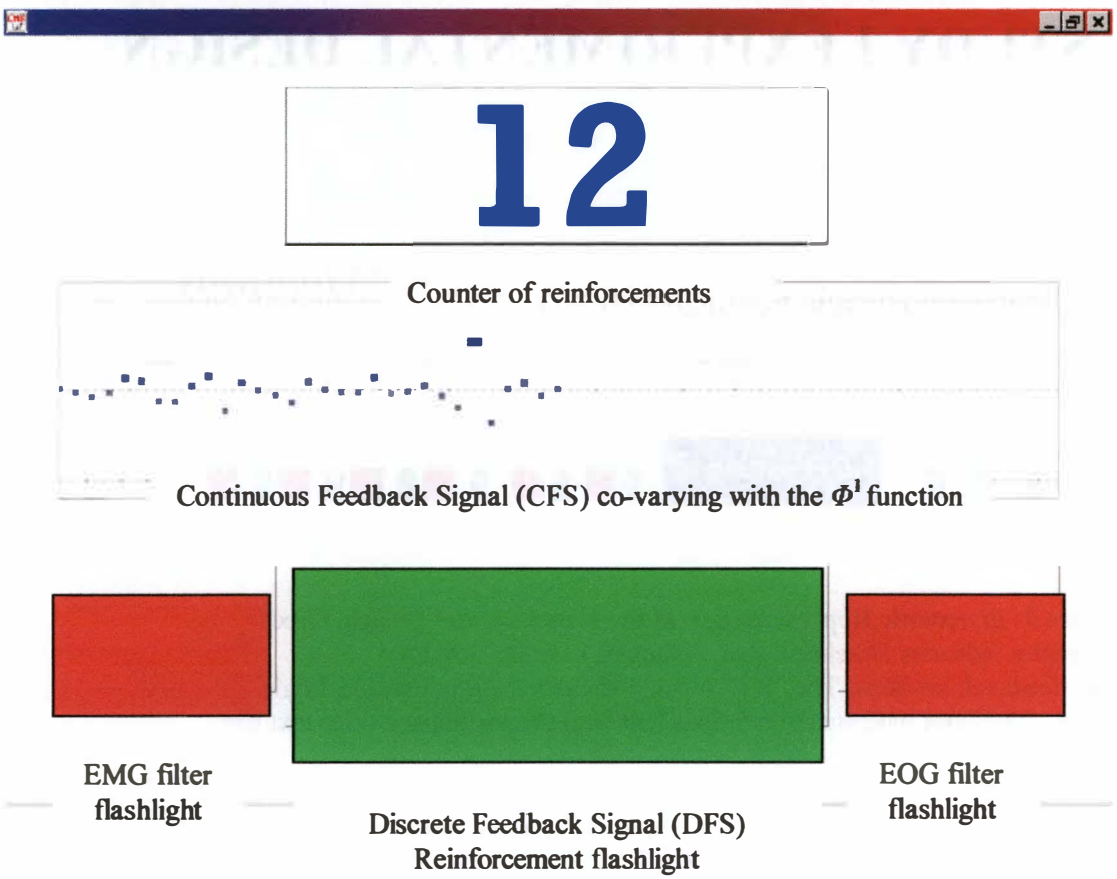


Figure 8. Snapshot of the LORETA Neurofeedback program interface. This is an example of the computer screen as seen by the participant during neurofeedback. The interface is controlled by the LNF program. The flashlights of the EMG inhibit filter, EOG inhibit filter, and the DFS reinforcement flashlight are shown in the "on" position. With these settings, they would turn white if in "off" position.

STUDY I EXPERIMENTAL DESIGN

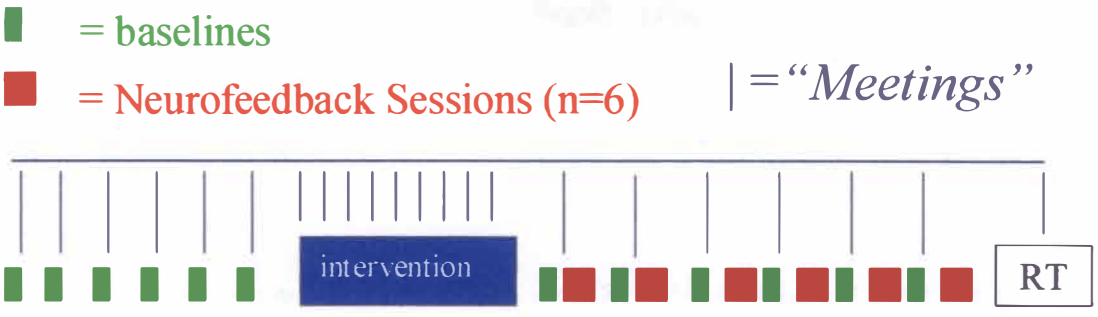


Figure 9: Schematic Representation of the Experimental Design. Green rectangles indicates Baselines. Red rectangles indicate LORETA neurofeedback sessions. The "RT" block indicates the Randomized Trials design. Blue lines indicate the meetings had with the participants. See text for details.

Table 1: Results of the Within Sessions learning hypothesis.
Learning curves of the β/α ratio over the six sessions. The Spearmann's correlations were computed using the EMG channel and the EOG channel as partial variable. P^+ and $P^\times$ are the additive and multiplicative combination of the three individual p-values respectively. Significant results are printed in green. Non-significant results are printed in red.

EOG and EMG partial variables

n=6	Subjects		
	I.1	**I.2**	**I.3**
Correlation	+0.839	+0.749	+0.630
Individual p-value	*0.170*	*0.250*	*0.369*

$P^+ = 0.081$;
$P^\times = 0.216$

Table 2: Results of the Volitional control learning hypothesis. Exact randomization ordinary least square (OLS) linear regression model. 2A: The full model testing the significance of the slope of the five dependent variables. 2B: Reduced model to test the hypothesis that the percent time spent in reinforcement state (%RS), the β/α ratio and the Φ^1 function are differ in trial "1" versus "trial "0", treating EMG and EOG as covariates. Significant results are printed in green. Non-significant results are printed in red. See text for details.

2B	Subjects				
	I.1	I.2	I.3	P+	P×
% RS	0.1	0.043	0.271	0.012	0.035
β/α	0.586	0.1	0.043	0.064	0.063
Φ^1	0.329	0.086	0.529	0.252	0.209
EMG	0.243	0.671	0.786	0.647	0.662
EOG	0.1	0.24	0.814	0.254	0.247

Full model

2B	Subjects				
	I.1	I.2	I.3	P+	P×
% RS	0.112	0.618	0.628	0.394	0.393
β/α	0.583	0.053	0.010	0.045	0.013
Φ^1	0.155	0.475	0.817	0.460	0.466
α	0.883	0.056	0.556	0.496	0.293
β	0.191	0.056	0.003	0.002	0.002

EOG and EMG partial variables

Appendix II

Subject Information

All information is confidential and will not be released to any person for any reason. Please answer as honestly as possible.

Initials: _____ File Name:_____
Age: _____
DOB: _____

Sex: (circle one) Male Female

Handedness: (circle one) Right Left Ambidextrious

Date/Time_____

Questionnaire

1. Have you ever had an injury to your head? _____
2. Have you ever been unconscious? _____
3. Have you ever been diagnosed with any mental disorder (this includes Depression, Anxiety, Schizophrenic, etc.)? _____
4. Do you currently or have you ever taken any psychotropic drugs? _____
5. Do you currently take any medications? _____
6. If so what medication and for what? _____
7. Have you in the past two weeks used any non-prescription drugs (marijuana, etc.)? _____
8. Do you have a history of alchoholism? _____
9. Have you ever been diagnosed with cerebrovascular disease? _____
10. Do you have a history of Migraines? _____
11. Have you ever been diagnosed with epilepsy? _____
12. Have you ever been diagnosed with a learning disorder and/or ADD/ADHD? _____
13. Have you ever been diagnosed with any type of sleep disorder? _____

Do you have one hour of spare time M/W/F either in the morning or in the afternoon? Please specify your availability_____

_____

This study will investigate your ability to change your brain-wave patterns in desired directions with the aid of feedback provided by a computer. It is only you that can achieve changes. The computer will not interfere with your brain activity. Please use the space below to explain your motivation in participating to this study:

Appendix III

Informed Consent Form

Informed Consent Form

Title of Project: ***Low-Resolution Electromagnetic Tomography Neurofeedback: A Pilot Study.***

Principal Investigators: *Joel Lubar, Ph.D., Marco Congedo, M.A.*

Objective of Project: The purpose of this project is to investigate your ability to change your brain electrical activity in specified directions. The data collected will help us to determine if it is possible to modify electrical activity of deep cortical structures.

Project Summary: You will participate in 30 training sessions. The training will consist of enhancing particular brain activities in selected regions of your cortex. Your electroencephalography (EEG) will be recorded continuously during each session. A computer will extrapolate meaningful information from your EEG and will give you feedback about your performance. You will be asked to obtain as much positive feedback as possible. Positive feedback will indicate that your brain activity is changing in the specified direction. The equipment will not influence directly your EEG activity, but will only provide you information. You might find the experience challenging or even frustrating, but you are asked to try your best on each session.

You will undergo standard psychometric testing before and after the training, so to allow us to assess cognitive performance improvements as a result of the training.

Your EEG will be recorded during each session. A three-minute eyes-closed baseline EEG will be recorded first, followed by the training session. Another three-minute baseline will be recorded at the end of each session. To record your EEG, an electrode cap with 19 sensors will be placed on your head. Electrode gel is applied to each sensor by a small tube inserted through the sensor. The gel forms a conductive pathway between the sensor and the scalp. There is no significant discomfort with this procedure either in the preparation or the wearing of the cap during the testing. An earclip electrode will be placed on each earlobe after a light cleaning with Omniprep solution, which removes skin oil and allows for good sensor contact. All creams and gels used during this evaluation are hypo-allergenic, with no known risk of irritation. Since muscle movements produce electrical activity which can contaminate the EEG, you will be asked to sit still, with eyes closed, in a relaxed posture.

You will be receiving extra-credit and a monetary compensation for participating in this study. The monetary compensation will vary depending on your learning performance and will be established according to the following rules: There will be a running balance updated at the end of each session. You will receive $10 for each session in which you showed improvements, while $5 will be subtracted for each session in which you showed poor performance. At the end of the last session the final balance will be established. Even if the final balance is negative, you will still receive a minimal payment of $50.

Amount of Time Required: Each session requires around one hour to be completed. There will be 30 sessions, three session per week during regular University of Tennessee hours.

Confidentiality: Only persons listed as Principal Investigators will have access to material that identifies you personally as a participant in this study. The data gathered during this experiment will potentially be shared professionally, but your name will be coded to prevent identification. These records will be stored in a locked file cabinet in the Brain Research and Neuropsychology Laboratory, A305 Walters Life Sciences, for at least three years past the duration of the study.

If you have any questions about this study, please feel free to ask them. Any future questions may be addressed to

Marco Congedo, M.A.
Department of Psychology
University of Tennessee, Knoxville
(423) 974-3222

or

Dr. Joel Lubar
Department of Psychology
University of Tennessee, Knoxville
(423) 974-3222 or 974-3360

Statement of Consent:: I certify that I have read and fully understand the procedures contained within this form and agree to participate as a subject in the research described therein. My participation is given voluntarily and without coercion or undue influence. I understand that I may discontinue participation at any time. However, I understand that students participating for extra credit will only receive credit and monetary compensation after completion of participation in the study.

Signature of Participant	Name of Participant	Date
Signature of Witness	Name of Witness	Date

Appendix IV

Form B

Form B

IRB# _____

Date received in ORC_____

THE UNIVERSITY OF TENNESSEE, KNOXVILLE

I. Identification of Project:

Date: September 1st, 2002

Project Director:	Joel F. Lubar, Ph.D. Department of Psychology 974-3360 or 974-3222
Co-Directors:	Marco Congedo, M.A. Department of Psychology 974-3222
Title of Project:	*Low-Resolution Electromagnetic Tomography Neurofeedback: A Pilot Study.*

Department:	Psychology
Starting Date:	Upon IRB approval
Completion Date:	May, 2003
External Funding Agency:	n.a.
Grant Submission Deadline:	n.a.

II. Objective of Project:

The purpose of this study is to investigate the effectiveness of Neurofeedback training of current density in the cerebral volume. Neurofeedback is an operant conditioning process by which the subject learns how to change his/her brain activity. The learning unfolds over several training sessions, usually 20 to 40. With the aid of real-time feedback provided by a computer the subject is able to continuously monitor his/her brain activity in selected regions and can learn to change it in wanted directions. Typically a rewarding condition is set at the beginning of the session. For example, the computer may be programmed to provide feedback any time the EEG power in the 10-13 Hz frequency band increases above 50 microvolts squared (uV^2). The computer then continuously extrapolates this measure from the EEG signal and provides visual and/or auditory rewards to the subject when the feedback conditions are met. The standard Neurofeedback is based on scalp potential electrical activity (Electroencephalography: EEG) and has been used regularly in this laboratory in the past 20 years. Low-Resolution Electromagnetic Tomography (LORETA) is a mathematical technique to derive intra-cerebral 3-D current density estimation from the scalp potential. It has been used worldwide in brain research since 1993. While scalp-recorded EEG consists of the superposition of the electrical activity of neurons located in brain tissue beneath the electrode, current density estimation refers to neurons electrical activity in specific brain anatomical areas. This allows the Neurofeedback process to be based on 3-D current source density instead of scalp potential and enables precise and specific training.

Clinical implications of the technique are potentially important, including the training of epileptic foci, language-related areas in the context of learning disabilities, attention deficit disorder, and in general any specific neo-cortical tissue.

While previous studies showed the effectiveness of the neurofeedback in the treatment of several neurological/psychiatric disorders, to our knowledge, no study to date has investigated 3-D current density neurofeedback.

III. Description of Subjects:

Subjects will be recruited from the Psychology Department Subject Pool. For specifics of the recruitment method please see Section V.

IV. Methods or Procedures:

We plan to execute a series of single-subject studies and to recruit a minimum of 2 subjects and a maximum of 8 subjects. Each subject will initially be screened for neurological and/or psychiatric status by means of a standard questionnaire previously used in other studies by this laboratory. Only those subjects who do not report any neurological/psychiatric disorder and who are not taking any psychoactive medication during the time of the study will be selected. On the basis of this selection, potentially suitable subjects will be asked to participate in the experiment. These subjects will be further interviewed in order to ascertain their motivation in participating in the study.

Subjects potentially included in the training sessions will be offered a variable amount of money to participate in the experiment. It will be explained to them that the total compensation they will receive for participating in the study will depend on their learning performance and that it might vary between $50 and $300. An objective criterion will be proposed for establishing the total compensation: there will be a running balance updated at the end of each session. Each participant will receive $10 for each session in which he/she showed improvements, while $5 will be subtracted for each session in which he/she showed poor performance. At the end of the last session the final balance will be established. Even if the final balance is negative, each participant will still receive a minimal payment of $50.

Those subjects who accept the offer will be initially presented with a *consent form*, which must be signed before the experiment begins. They will also undertake a *preliminary EEG evaluation*, which will be performed by standard data analysis procedures employed in this laboratory. The subject's EEG features will be compared with a normative database in order to assess his/her deviance from normative EEG values. This information may be used for establishing the neurofeedback protocol (see below).

The training will consists of 30 1-hour sessions. Sessions will start after the first day of classes and will be completed by the last day of classes within each semester. The sessions will take place in a sound-attenuated room of our laboratory.

During each session the EEG will be acquired continuously following the International 10-20 system for electrode placement. Hookups will be made using an electrode cap (Electro Cap Inc.) and Electrogel conductive cream (Weaver and Co.). Subjects will have the electrode cap with 19 sensors placed on their heads. Electrode gel is applied to each sensor by a small tube inserted through the sensor; the gel forms a conductive pathway between the sensor and the scalp. There is no significant discomfort with this procedure either in the preparation or the wearing of the cap during the testing. Two earclip electrodes will be placed on the earlobe after a light cleaning with Omniprep solution, which removes skin oil and allows for good sensor contact. EEG data will be collected during the experimental procedure by means of a Neurosearch-24 (Lexicor Medical Technologies) analog to digital EEG data acquisition device.

Once this cap has been put in place, the electrode impedance will be tested with an impedance meter (Grass Medical Technologies) and adjusted below 5 Kohms. At this stage a 3-minute eyes-closed pre-baseline will be recorded. A minute later the training session will start. The subject will be seated in a comfortable chair in front of a computer screen and will be instructed to try to obtain as much feedback as possible. Feedback signals may consist of tones emitted from the computer and/or graphical patterns (bar or line graphs) on the computer screen. Each training session will last 20 minutes. Finally, a 3-minutes eyes-closed post-baseline will be recorded. At the end of the second baseline the EEG recordings will end. The cap will be removed, and the electrode gel, which is very similar to hair mousse, will be wiped off with a tissue or paper towel. All creams and gels used during this evaluation are hypo-allergenic, with no known risk of irritation. The entire procedure for each session should be completed in one hour. Our laboratories have used this method of application in previously approved projects since 1985.

Training protocols employed in this research will be either subject-by-subject based or fixed. On the basis of the preliminary EEG evaluation (see above) the protocol may involve the

normalization of extreme EEG features (as compared with the normative database) of the subject. Fixed protocols that may be used are the Theta Power enhancement in the anterior cingulate and the alpha power enhancement in the right prefrontal cortex. A large body of literature suggests that frontal midline theta (generated in the anterior cingulate) is involved in working memory cognitive tasks. Enhancing Theta power in this region should improve working memory skills. Right prefrontal cortex activity, on the other hand, has been repeatedly associated with anxiety and negative feelings. Since Alpha power is inversely related to brain activity, enhancing Alpha power in this region should improve mood and reduce anxiety.

Standard psychometric evaluation will be performed on each subject before and after the training. The goal is to assess changes in cognitive performance. Tests employed will be the STROOP, IVA (Integrated Visual and Auditory Attention Test), and the WAIS (Wechlser Intelligent test for adults, selected subtests for working memory). Psychometric tests will be administered by or under the supervision of Teresa Hutchens, counseling psychologist with over 20 years of experience in neuropsychological testing.

V. Specific Risk and Protection Measures:

EEG data acquisition and LORETA neurofeedback training sessions will be performed in the Brain Research and Neuropsychology Laboratory, namely by Dr. Lubar and Mr. Congedo. Scalp EEG neurofeedback presents minimal risk to human subjects. It has been used in this laboratory over the past 20 years and no case of harmful effects have been reported. LORETA neurofeedback is in principle equivalent to scalp EEG neurofeedback, with the exception of its spatial properties cited above (II). To our knowledge, no previous research has been using this paradigma.

Recruitment. Subjects will be recruited via the Psychology Department Human Subject Pool, and will receive extra credit according to the agreement between the Psychology Department and the Human Subjects Research Committee. Sign-up sheets will be posted in the designated area of Austin Peay Building, and teachers will be asked to make announcements.

Procedures to Maintain Confidentiality. Names, telephone numbers, and scores of all subjects will be recorded in our files. These records will be stored in a locked file cabinet in Room 305D of Walter Life Science Building. Access will be restricted to Dr. Lubar, and Mr. Congedo. Data entry (into the computer data file) will not include names or other identifying information. Immediately following data input, the hard copies of names and other identifying information will be destroyed via shredding. Confidentiality will be maintained with respect to the EEG data because only subject ID numbers will be used.

VI. Benefits vs. Risks:

Benefits to the students for doing this study include monetary compensation and extra-credit for participation. An additional benefit will be the advancement of knowledge in the field

of EEG research. The risk to either physical or psychological well being of any subject participating in this study is minimal. At the beginning of each session subjects will be told that they can withdraw from the study if they feel uncomfortable at any time without penalty.

VII. Methods of obtaining "Informed Consent" from subjects:

Subjects who meet the criteria and who are suitable for inclusion in the experimental groups will be offered monetary compensation (see IV) to participate in the training. Those subjects who accept the offer will be initially presented with a consent form, which must be signed before the experiment begins. All subjects will be required to read and sign the informed consent form (see attached Consent Form) prior to participating in each of the parts of this study.

VIII. Qualifications of the Investigators:

Dr. Joel Lubar is a Full Professor in the Department of Psychology at the University of Tennessee, and has over 35 years of experience working in the field of neuroscience. He is a licensed Psychologist within the State of Tennessee, with the designation of "Health Service Provider."

Marco Congedo is a Ph.D. candidate in the Experimental Psychology Program at the University of Tennessee. He received his bachelor's degree in psychology from the University of Padua in Italy in 1998, and his M.A. degree in experimental psychology from the University of Tennessee in 2002. He has three years of practice administering EEGs and running neurofeedback trainings.

IX. Adequacy of Facilities to Support Research:

The physical requirements for carrying-out the training sessions in this study are completely adequate. The Psychology Department at the University of Tennessee has the requisite space and computer equipment for implementation.

Data collection and training sessions for this study will be accomplished within the Brain Research and Neuropsychology Laboratory. Walter's Life Sciences Building, University of Tennessee. Equipment to be used is owned by either Dr. Joel Lubar, or the University of Tennessee. All instrumentation and test materials to be used in this study are directly comparable to materials used in hospitals and clinical settings.

X. Responsibility of Project Director:

By the Compliance with the policies established by The University of Tennessee,

Knoxville, Committee on Research Participation, the project director subscribes to the principles stated in "The Belmont Report" and standards of professional ethics in all research, development, and related activities involving human subjects under the auspices of The University of Tennessee, Knoxville.

a. Approval will be obtained from the University Committee prior to instituting any change in the research project.
b. Development of any unexpected risks will be reported to the University Committee.
c. A status report (Form D) will be submitted at 12-month intervals or as requested attesting to the current status of the project.
d. Signed consent statements will be kept for the duration of the project and for at least three years thereafter.

Project Director: _____
Joel F. Lubar

Date: _____

Co-Director: _____
Marco Congedo

Date: _____

XI. Departmental Review and Approval:

{omissis}

Vita

Marco Congedo was born in Bari, Italy, on the 20th of October 1972. He attended the University of Padua (Padova, Italy), where in 1998 he received the B.A. degree in Psychology. In 1996-97 he prepared his undergraduate thesis at the University René Descartes, Paris, France, under the supervision of Dr F. Askevis. In 2001 he received his M.A. degree in Biological Psychology from the University of Tennessee, where he has been studying since 1999 with Dr. J. Lubar.

He speaks fluently in English and French, in addition to his mother-tongue (Italian). While he was a graduate student at the University of Tennessee, Marco Congedo published three papers in peer review editorial journals and received several scholarships and research grants. In May 2003 he was awarded twice from the Department of Psychology of the University of Tennessee for excellence in Scholarship and Graduate Research.