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A New Neurofeedback Protocol for Depression

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Context: Neurofeedback represents an exciting complementary option in the treatment of depression that builds upon a huge body of research on electroencephalographic correlates of depression. Objective: The objectives of this article are threefold: review the literature on neurofeedback protocols for depression; introduce a new protocol, which aims to synthesize the best qualities of the currently available protocols; and present the results of a small clinical experiment with the new protocol. Method: Structured survey of the literature; software development; clinical trial with one subject, submitted to ten sessions of neurofeedback (one hour each). Results: Currently there are twenty-one articles in neurofeedback for depression, among which only six present original experimental results. All of them report positive results with the technique. The most used protocols focus on Alpha inter-hemispheric asymmetry, and Theta/Beta ratio within the left prefrontal cortex. Our new protocol integrates both dimensions in a single circuit, adding to it a third programming line, which divides Beta frequencies and reinforces the decrease of Beta-3, in order to reduce anxiety. The favorable outcome of our clinical experiment, suggests that new research with this protocol is worthwhile.
Keywords: depression, neurofeedback, software development, clinical trial.

Contexto: El neurofeedback representa una excitante opción complementaria para el tratamiento de la depresión que se basa en un enorme cuerpo de investigación sobre los correlatos electroencefalográficos de la depresión. Objetivo: Los objetivos de este artículo son varios: revisar la literatura sobre los protocolos de neurofeedback para depresión; introducir un nuevo protocolo que pretende sintetizar las mejores cualidades de los protocolos actualmente disponibles; y presentar los resultados de un pequeño experimento clínico con el nuevo protocolo. Método: Inspección estructurada de la literatura; desarrollo de software; ensayo clínico con un participante sometido a diez sesiones de neurofeedback (una hora cada sesión). Resultados: Actualmente hay veintiún artículos sobre neurofeedback en depresión, entre los cuales solo seis presentan resultados experimentales originales. Todos ellos reportan resultados positivos con la técnica. Los protocolos más usados se centran en la asimetría inter-hemisférica de Alpha, y la razón Theta/Beta dentro del cortex prefrontal izquierdo. Nuestro nuevo protocolo integra ambas dimensiones en un solo circuito, añadiendo a una tercera línea de programación, que divide las frecuencias Beta y refuerza el decremento de Beta-3, con objeto de reducir la ansiedad. La consecuencia favorable de nuestro experimento clínico sugiere que nueva investigación con este protocolo es aconsejable.
Palabras clave: depresión, neurofeedback, desarrollo de software, ensayo clínico.

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'Depression' is a broad and popular concept that has been widely used in reference to a state of diminished humor that stands beyond the relationship which one draws with specific stressors. The intensification and recurrence of this state gives birth to major depressive disorder (MDD), which is a much more specialized concept that psychologists and psychiatrists use to refer to a disabling condition that not only include the aforementioned (low) mood symptoms, but several other mental and organic manifestations (Lewis, 1934), ranging from neurovegetative abnormalities to cognitive and problem-solving deficits (Hamilton & Gotlib, 2008).

The most well-known models of MDD neurobiological basis focus on the neurochemical dysfunctions that accompany its phenomenological manifestations (of which the monoaminergic hypothesis is the most traditional: Delgado, 2000). Recently, alternative models have been proposed; with a special emphasis on the disorder's electroencephalographic (EEG) correlates. This new perspective opened a venue to the use of EEG for diagnostic and prognostic purposes, producing a new hope and excitement among patients and health practitioners, commonly seen today. In 2003, an article published in a journal of the "Nature Group" pointed to the possibility of using an electroencephalographic marker, discriminated in REM sleep, as a predictor of therapeutic success of subsequent pharmacological treatment (Murck et al., 2003). In 2006, another study demonstrated the possibility of using EEG to predict the potential effects of different antidepressants (and thus to define the pharmacological treatment of choice), 48 hours before any perceived effect (Hunter, Leuchter, Morgan, & Cook, 2006). Also, in 2008 it was found that a very simple electroencephalographic marker (Alpha asymmetry) could be used to predict the response to antidepressants before the beginning of the pharmacologic treatment, in such a sense that it could serve as an aid in the choice of treatment (Bruder et al., 2008).

We recently conducted a review of the literature, which revealed the existence of at least 60 articles indexed in PubMed, addressing the relationship between several of depression's nosological dimensions and electroencephalographic patterns (e.g., sleep patterns) and an equivalent number of articles taking depression as a whole and linking it to EEG markers.

Unfortunately, this literature also reveals the existence of a certain lack of conceptual and methodological consistency, which makes convergent findings appear divergent and vice versa. For this reason, we would like to initiate this article with some introductory notions that are necessary to the proper understanding of our results and of the literature as a whole. The EEG is organized in frequency bands with differing amplitudes. The canonical literature on the matter defines Delta and Theta bands as slow, Alpha as intermediary, and Beta and Gamma as fast frequency bands. Regarding the predominance of these frequency bands, it is known that greater Alpha activity on the left hemisphere is correlated with the inhibition of local neural networks, and hence that the EEG is asymmetric to the right. Conversely, stating that a brain map (QEEG) is asymmetric to the left, means that Alpha predominance is found on the right hemisphere (Klimesch, Sauseng, & Hanslmayr, 2007; Schmidt & Hanslmayr, 2009).

In summary: the statement that a particular EEG shows "left asymmetry" is opposed to the claim that the EEG has an "asymmetry in Alpha to the left". In our opinion, this potentially confusing situation suggests that it could be worthwhile to limit the application of the concept of "asymmetry" exclusively to the first case, whereas the second condition could be better defined by the use of the expression "(Alpha) predominance"- an option that we will heretofore adopt and apply to the discussion of the literature of interest that could otherwise generate doubts on this matter.

With these distinctions in mind, Harmon-Jones concluded that: "frontal asymmetry is correlated to the motivational direction" (Harmon-Jones, 2003, pg. 846). This conclusion can be associated to the existence of a positive correlation between left Alpha EEG predominance and positive scores in behavioral activation tests (Coan & Allen, 2003), and to the existence of a correlation between right asymmetry and elevated scores in different depression scales (Diego, Field, & Hernandez-Reif, 2001). Also in the same sense, a recent meta-analysis, based on thirty-one experimental studies, concluded that both depression and anxiety are related to right prefrontal asymmetry (Thibodeau, Jorgensen, & Kim, 2006), therefore endorsing the perspective that an excess of Alpha activity on the left side of the brain is related to subjective processes and behaviors characterized by negative valence.

Conversely, a recent study with a cohort of elderly diagnosed with MDD concluded that "a relative greater activation on the left (in this case, of Alpha) relates to lower Beck scale scores. This, however, is correlated only within the normal group." (Deslandes et al., 2008, p. 321). As this last study suggests, there are subtle perspectives that need to be established in relation to the electrophysiological correlates of the different manifestations of depressive symptoms (i.e. reactive vs. chronic), in relation to different populations. In order to properly establish all these subtle perspectives, and boost the development of the field, several brain mapping (QEEG) databases have been developed and extended. These databases store EEG data from thousands of subjects, with different and carefully discriminated profiles, providing the opportunity to study normal and abnormal electrophysiological brain patterns. One of the databases that stands out is of the New York University, accessible at: http://www.med.nyu.edu/brl/research/technology/qeeg_database.html.

As we gain insight on the relationship between depression (and anxiety) and EEG patterns, the use of EEG

as a treatment tool also becomes a more popular avenue of query. Such an application occurs mainly through (1) the process of mapping brainwave patterns, in order to define the EEG correlates of given clinical complaints; (2) the use of specific protocols, based on the discrimination of these EEG abnormalities, to stimulate the client to increase or decrease power in specific EEG bands, as read from electrodes positioned over specific areas on the scalp. This technique is denominated 'neurofeedback' or brain wave biofeedback.

As with any form of biofeedback, neurofeedback is built upon the self learned practice of conscious generation of more healthy organic patterns. The technique represents a form of operant conditioning, through which an individual may learn to modify the electrical activity of his own brain (Thatcher, 2000). It is widely believed to be free of health risks, although it is important to determine with caution the presence of paroxysmal activity in the frequency bands to be amplified, in order to avoid the amplification of the same paroxysmal phenomenon.

Detailed electroencephalographic studies demonstrate that the technique is capable of generating long term alterations in the spectral EEG topography (Egner, Zech, & Gruzelier, 2004), while neuroimaging studies reveal the existence of neuroplastic effects from neurofeedback training (Levesque, Beauregard, & Mensour, 2006; Ros, Munneke, Ruge, Gruzelier, & Rothwell, 2010). Finally, DeRubeis and collaborators, in a recent article published in Nature, defined neurofeedback for the treatment of depression as having "revealed promising effects in recent clinical trials" (DeRubeis, Siegle, & Hollon, 2008, p. 789). We share much of this enthusiasm, but add that the field still has space for substantial evolution, especially in regard to the elaboration of new and more complete training protocols that may be capable of maximizing this potential.

Objectives

This paper has three intimately related objectives, which are organized so that each step serves as an introduction to the next. Initially, a short, structured revision of the literature on neurofeedback for the treatment of depression follows. This first step seeks to assess the reported efficacy of the technique and to describe the most supported EEG protocols.

In light of the conclusions relative to these reviewed protocols, we introduce a new computerized neurofeedback protocol for the treatment of depression that integrates the main advantages of the presently existent protocols and that resolves a potentially limiting methodological question. In this stage, we present the central aspects of the protocol, providing the reader with an objective measure for the innovation to be offered, as well as with some familiarization with the operational modes of the "circuits" that describe the brain-computer interface (BCI) of which this technique makes use.

Finally, we introduce the results of a small clinical trial, which evaluates whether depressive patients could actually benefit from our new protocol that involves simultaneously training multiple neurophysiologic demands. As we assess it, the extent to which the protocol proves to be successful defines the extent to which it could be considered as an improvement upon the currently available ones. The publication of this article aligns itself with the authors' commitment to make the system publicly available (in: http://creativecommons.org/).

Method

Review of the Literature

The review took place in October, 2009. With the aim of establishing a base upon which the efficacy of the technique could be to assessed and to define the main training protocols presently in use, the following procedures were applied: first, using the keywords "neurofeedback and depression," PubMed, PsycINFO and Google Scholar database were prospected and the relevant publications were downloaded and stored in a private database. The references contained in these publications were used to search for other, equally relevant, publications.

In a second moment, the text and data mining software RefViz (Thomson Research) was used to simultaneously scan the following databases for more relevant studies: Web of Science, Purdue University, OCLC Medline, OCLC Eric, OVID Medline and PubMed. At this second moment, we used the keywords "neurofeedback or neurotherapy", in order to expand as much as possible our chances of finding relevant studies.

With these results in hand, we read all the abstracts and selected potentially relevant publications to be analyzed in full extension. In all cases, we discarded all publications that were not peer reviewed articles (conference abstracts and book chapters were not included). While reading our results, one should bear in mind that the scarcity of studies does not permit a meta-analysis.

New Protocol

The development of the new neurofeedback protocol for depression took several months, during the year of 2009 and was based upon the use of the graphic interface for digital signal processing provided by the software BioExplorer (CyberEvolution, Inc.). This software offers a graphic programming environment, in the form of a flowchart or "circuit", which aggregates all the necessary programming levels onto one single level, thus providing a visual integration of all the variables necessary to the proper operation of the protocol.

In practice, this means that we programmed in a single hierarchical level, all aspects of the design, from the

calibration of the electrophysiological signals arising from multiple data channels, on through all the data stream and temporal modifications, adding conditional requirements for successful training and continuing on through the interfaces designed for the intermediation between the patient and computer (BCI). As mere introductory information, we point out that this final intermediation is the basis for the training of intentional control over physiological variables. The protocol's interface is programmed to allow media to respond with direct correlation to the electrophysiological signal readings. For example, the patient may train watching a movie of his choice (in DVD or MPEG video format) where the audio volume or screen brightness and size are in fact controlled by the electrical activity captured by electrodes and processed in the computer program. The changes occurring in the person's electrodynamics are reflected in the volume and screen size/brightness of the movie being watched.

Clinical Experiment

This clinical trial has a strictly preliminary character, serving solely to offer a initial evaluation of this new protocol's potential. Training sessions were conducted with one female subject, 42 years of age, with a recent diagnosis of depression. The subject had no history of other psychiatric disorder, nor was she using any psychiatric medication, though she did maintain a medical regimen of Tamoxifen (estrogen antagonist) in prophylactic treatment for malignant ovarian neoplasm. In total, the presented data considers the first 10 sessions of neurofeedback of one hour duration each (two sessions per week), conducted between the days of July 21st until September 4th 2009, during which self-assessment of performance and symptomatic evolution was tracked.

A two channel, bipolar montage was used with active electrodes over the F3 and F4 active sites ("10/20" system) and with linked auricular references. The use of this montage was based upon the strongest tradition in the field for neurotherapy for depression, the protocol ALLAY by Rosenfeld and collaborators (for the patent: Rosenfeld, 1996), wherein Alpha asymmetry is precisely focused upon at F3 and F4 (Baehr, Rosenfeld, & Baehr, 1997). Throughout the entire training procedure, the electrical impedance at the electrode sites was maintained below 5kΩ; the hardware band pass (frequency band) was 1-50Hz; the ground was placed at FZ.

The analog to digital signal processing and the signal amplification was carried out automatically within the electroencephalogram unit, model "A3", manufactured by the Minder Labs PL ACN company (Sidney, Australia), where two independent EEG channels were used at a sampling rate of 256 samples per second, each with a 10bit resolution and a wireless communication protocol of 2.4GHz. Due to the peculiarities of the Brazilian electrical grid, a "noise" reducing 60Hz notch filter was applied between 59 and 61Hz.

BioExplorer software was installed on a portable computer with a 2.0 GHz processor and 2.0 Gb of memory RAM. The incoming EEG data was processed using the Fast Fourier Transform; the processed data refers to the relative amplitude of the EEG when separated in the different wave bands.

Depression diagnosis was obtained from a directed interview (First et al. 1996) previous to the experiment; the patient was also previously submitted to the Hamilton Depression Scale to assess the severity of the disorder (Hamilton, 1960). During the initial session and throughout the nine subsequent sessions, the patient maintained a system of neuropsychological self-assessment (of our authorship) that provides a subjective indication of the technique's effect.

This questionnaire is based on forty seven symptoms/items, extracted from the main neuropsychological batteries applied in affective disorders. Initially the subject rated all forty-seven items and defined the intensity of each one of the symptoms that she found to apply to her experience (in 8 degrees of intensity: 0-7). Subsequently the seven most prominent symptoms were used for ongoing tracking and evaluation, always at the beginning of each new session, before training began on that day and always blinded to previous responses.

A macro of our authorship lists and exports these most severe symptoms (in association with its respective degree of intensity) to a separate table from which a clearer vision of the case and its evolution emerges. The description of the method and its programming basis has not been published yet, but it comes serving several psychologists and psychiatrists in Brazil who, during the past two years, have been adopting our methodology of neurofeedback training for the treatment of psychiatric disorders. That said, it is to be considered that this method was only used with the aim to assist the principal source of diagnosis (which was the directed interview) and should not be taken as our primary source of nosographic knowledge about the patient/subject of this experiment.

A brain map was also generated for the evaluation of the benefit of the new protocol to the demands present in the EEG. The data for the brain-mapping analysis was obtained bilaterally from the following areas: prefrontal cortex; central sulcus (on the sensorimotor cortex); parietal cortex; temporal cortex and the sagittal inter-hemispheric fissure (in the terminology of the EEG technique: F3/F4; C3/C4; P3/P4; T3/T4; FZ/OZ) following a "mini-QEEG" methodology developed for low cost EEG assessment by The Learning Curve, Inc. of Lancaster, Pennsylvania.

This mapping disclosed EEG patterns that are suggestive of diminished motivation (Coan & Allen, 2004) and depressive trends, but that not necessarily characterize the presence of major depressive disorder - at least in

accordance with the previously mentioned criteria of Alpha asymmetry to the left as the main EEG marker of depression (Baehr & Baehr, 1997; Diego, Field, & Hernandez-Reif, 2001). In other words, the patient had an EEG that was asymmetric to the right (left Alpha predominance), but this was not as pronounced as in some of the above cited studies. The training was carried out by means of a bipolar montage with active electrodes over F3 and F4, following standards used in the field (Baehr, Rosenfeld, & Baehr, 1997).

Results

Review of Literature

The manual search for articles on neurofeedback for depression resulted in 20 retrieved papers, among which only 6 were found to present original clinical data. The use of text and data mining methods was of no value in this occasion. Within these findings, one exclusively involved patients with depression in comorbidity with alcoholism (Saxby & Peniston, 1995), while the other five described non-controlled clinical trials of short duration (Baehr & Baehr, 1997; Baehr, Rosenfeld, & Baehr, 1997; Baehr, Rosenfeld, & Baehr, 2001; Earnest, 1999; Hammond, 2000). Objective measures of efficacy of neurofeedback training could not be established with exactness, due to methodological limitations of these studies. With these limitations in mind, one should note that the results were found to be encouraging; for instance, one trial reported a five year post-treatment follow-up, disclosing lasting effects of the training period (Baehr, et al., 2001), while another one, through a follow up of two years, pointed to an effectiveness of 92% of neurofeedback for depression in comorbidity with alcoholism (Saxby & Peniston, 1995).

All of the studies involved few subjects (the most extensive involving fourteen subjects: Saxby & Peniston, 1995), and also all concluded that the application of the technique had attenuated the clinical signs of the depression. These results go hand in hand with our clinical experience, at the same time that they evidence the necessity of newer and more robust studies.

In order to establish the protocols that are been mostly indicated for the treatment of depression, the findings prospected with "data mining" were quite useful. By this method we could shed light into 12 articles that, as a set, corroborate the existence of two basic clinical tendencies: rewarding inter-hemispheric Alpha asymmetry (Angelakis et al., 2007; Baehr & Baehr, 1997; Baehr, et al., 1997; Baehr, Rosenfeld, & Baehr, 2001; Hammond, 2005; Saxby & Peniston, 1995) and rewarding the reduction of the Theta/Beta ratio in the left pre-frontal cortex (Gruzelier & Egner, 2005; Michael, Krishnaswamy, & Mohamed, 2005).

The first trend focuses on the inversion of the commonly observed Alpha predominance to the left in depression, by training Alpha predominance in the right prefrontal cortex and decrease of Alpha activity in the left prefrontal cortex; it is the most mentioned protocol in this literature: "Findings from diverse studies examining the spectral EEG suggest the existence of diminished left prefrontal activity in individuals with depression, both in relation to right frontal activity, as well as in relation to the left prefrontal EEG activity in healthy individuals" (DeRubeis, et al., 2008; p 791).

The second trend is relative to the reduction of Theta activity (4-8 Hz) in relation to Beta (15-28) in the left prefrontal cortex. Beta activity is related to executive and motivational functions, both of which are negatively affected in depression, possibly in association with prefrontal hypo-activation (DeRubeis, et al., 2008). It is to be noted that this pattern is not contradictory with the previously stated one, but instead potentially complementary to it. Considering the right/left inter-hemispheric relationship in regard to Alpha, the perspective now is to obtain increased Beta activity in the left hemisphere. This growth is related to a boost in executive functioning, which explains why it is also being indicated in the treatment of attention deficit (for a current meta-analysis: Arns, de Ridder, Strehl, Breteler, & Coenen, 2009).

Protocols related indirectly to the treatment of depression also exist, such as the protocol of Eugene Peniston for the increase of the amplitude of Alpha and Theta, which focuses on the treatment of chemical dependence and alcoholism, while it represents an attempt to reduce anxiety. In any regard, we believe that it is not prudent to include Peniston's protocol among the protocols indicated for the treatment of depression, given the lack experimental basis for such and given the fact that it seems intuitive that an increase in Theta activity could lower brain activity in general, turning out to be counter-productive to depressive patients.

Finally, considering the protocol of Beta increase, we add that the close relations and recurrent comorbidity of depression and anxiety implies the necessity for careful programming in order to eliminate the possibility that a training protocol for depression lead to increased anxiety. To this end, the definition of specific Beta bands becomes preeminent, as will be argue in the next section.

New protocol

Our review of literature revealed the inexistence of any system presently capable of integrating the two described basic protocols, in that such integration seems attractive (if not self-evident) as each one is associated with a specific EEG facet of depression. To fill this void, a new computerized protocol was developed, simultaneously capable of providing the training demands of Alpha asymmetry and increased Beta/Theta relationship in the left prefrontal cortex. This protocol also proposes a resolution to the potential quandary represented by the perspective

that Beta training could lead to anxiety: when establishing the training section within the Beta frequency band, an independent condition was created to the reduction of higher frequency "Beta 3" or "hibeta" activity (23-38 Hz) in both hemispheres, while reinforcing through training "Beta 1" (15-20 Hz) on the left hemisphere. In that sense, the protocol presents three parameters for the brain to train: increase of the asymmetry of Alpha (9-14Hz) to the right, increase of the Beta/Theta relationship (Theta 4-8Hz) on the left prefrontal cortex, and reduction of the Beta 3 component (23-38 Hz) over the entire prefrontal cortex.

In accordance with its objectives, the new protocol possesses three zones of programming that respectively address: direction of the subjective experience and behavior toward a more positive valence (Baehr, et al., 1997 positive; Baehr, et al., 2001); improvement of cognitive and motivational functions (Thompson & Thompson, 1998), and anxiety reduction (Saxby & Peniston, 1995). We present below (figure 1) the programming interface ("signal diagram"), in which the conditions implemented can be visually located:

This software "circuit" is the essence of the protocol and can be used with more than 10 different 2 channel EEG devices; more so, its functional logic can be adapted into many other existing programmable brain interfaces, thus justifying its presentation within the creative commons. We support the initiative of those who want to copy it, in part or integrally, while its commercialization is not authorized.

Our protocol can be used with any type of available feedback. Merely download the template and open in one of many existing compatible EEG softwares (i.e., BioExplorer), then associate each one of the parameters to a type of feedback (i.e., associate increased Beta/Theta with increase of screen brightness; Alpha asymmetry with a pleasant sound and increased Beta 3 with sound-blocking functions or with a less agreeable sound). In all feedback formats, as can be seen from the example, we suggest two compensatory feedbacks and one detractor or mild aversive in order to encourage the increase of the Beta/Theta ratio distinct from an increase in the Beta 3 that we want to prevent due to its association with anxiety.

To easily grasp the general logic of the programming, we suggest locating the two data sources in Figure 1, graphically representing the two electroencephalograph channels by their orange color. These sources feed the groups of filters, switches and temporal conditions represented by objects with clear gray color and follow through by definition to a set of objects that can be re-scripted (that we customize in accordance with subject feedback preferences), providing the subject's interface, represented by the dark gray color.

In further detail, our programming circuit divides itself in three parts (three bands/horizontally displayed), which are very similar in appearance from one to another. In the upper part one can see the filter-set and training subsystem for increase of the Beta predominance and the Beta/Theta amplitude relationship in the left hemisphere that conjoin in the training object ("Threshold 1, Left Beta success"). In the central part we find the filter-set and training subsystems for the reduction of amplitude in the Beta 3 frequency ("Threshold 4, Beta3 reduce"); and in the inferior part we find the same for the alpha asymmetry ("Threshold 2," "Right Alpha success"). Finally, the three parts are integrated by the central object ("Threshold 3, All Success") which is precisely the fulcrum of our circuit, as well as the parameter for performances assessment, as it generates a positive output dependent on the integration of the three separate training requirements we employ.

Initially, the circuit calibrates the entrance of the signal ("Source 1/EEG," on the top left and "Source2/EEG" on the bottom left) to prepare the raw signal by means of filters ("Expression 1 and Filter 1", in the upper part of the figure). From this point, the streams of continuous values acquired are converted into discrete values and begin to serve as a basis for baseline capture ("Expression 4"). Also present in this design are time capture objects for the diverse functions that we establish, which track performance assessment: total time of each condition; actual time necessary for the definition of the baseline ("Expression 4" is a conditional 60 seconds dependent upon the accumulated "Threshold 3" time passing); counting of the time the signal was above/below the base line ("Expression 7") and other time cycles of secondary importance.

Considering the natural inter-individual variation in the standard EEG, in light of the intent to use with many persons and derive a protocol metric, the normalization of raw amplitudes becomes necessary. This is achieved in the following manner: if the computed emergent signal is equal to the baseline, a '0' value is attributed to that relationship. When the signal is different from the baseline, the integer curve generated from said signal variation as compared to the fixed baseline generates a positive integer when signal moves in the desired direction as compared to baseline and a negative one when opposite the desired direction. This provides a standard number range with positive for desired and negative for undesired in order to serve the subject and the researcher in training and consistent reporting.

Following along to the far right of the circuit one may note that, counting from top to bottom, the third object down on the signal diagram, named "All Bell Count," has a bright green dot, signifying the exportation of data to the statistical set. This object receives commands directly from the conditional "Expression 5/All Success" that in turn receives data from "Threshold 3/All Success." In practice this is the main condition, consolidating all individual conditions required of the subject. Further, when maintaining the three electrophysiological parameters within their training threshold for a five hundred millisecond duration, an increasing tone "harmonic" (bell) is played, serving to reward and/or indicate movement in the correct direction. In behavioral terms this informs the subject positively that she has surpassed his or her own limits, since the threshold is established by the subjects own dynamic baseline.

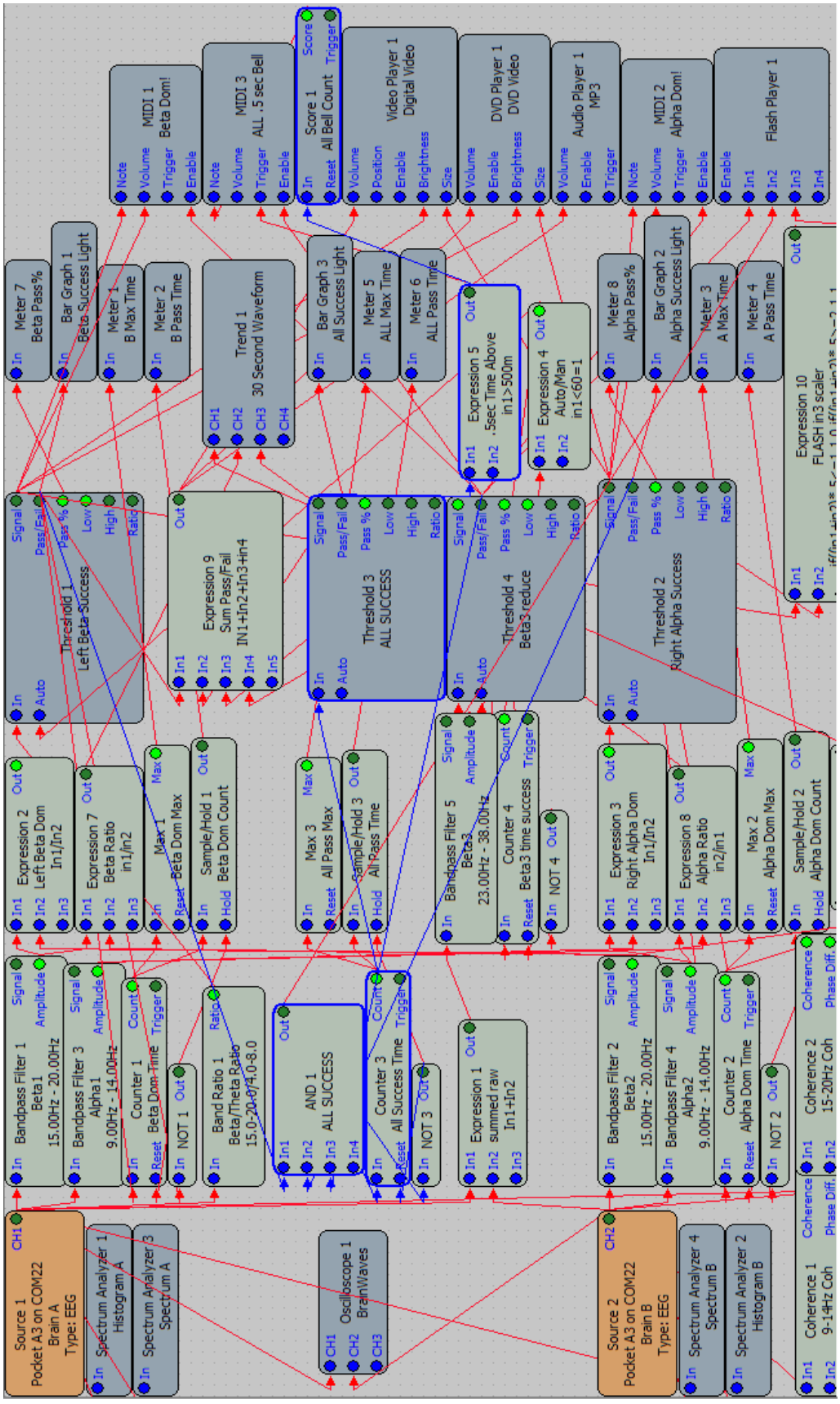

Figure 1. New neurofeedback programming design to the treatment of depression. This piece of software introduces illustrative programming boxes that can be manipulated intuitively.

Clinical experiment

In thesis, the potential of this new protocol is self evident: the integration of three demands correlated with three brain electrophysiological patterns, which psychophysiological studies point out as lacking separately in depression, can bring about better results than any one of them alone. In practice, things are not always so simple and empirical tests become necessary to test the thesis. To this end we carried out a small clinical experiment that serves as a first test for the evaluation of the potential utility of the new protocol, while it responds to the hypothesis that depressive patients are able to interact with a system of more complex electrophysiological demands as they do, when each one of the protocols is used separately.

As described in the section "methods," this stage recounts the results of 10 sessions of neurofeedback of one hour of duration each, using a two channel, bipolar montage, with active electrodes over the areas F3 and F4. Given the scarcity of studies in neurofeedback for depression, it is to be considered that this experiment also serves as a clinical resource, despite express disclaimer of any intention to validate new clinical methods with small, uncontrolled case reports.

Assessment

As we describe in the section "methods," the diagnosis basically involved a directed interview. Throughout the training we use a self assessment questionnaire to characterize the experience of the patient. In parallel, we use a multisite brain map to evaluate whether the demands of the subject would be adequate to what the new protocol provides.

In figure 2 (see below), we present key detailed results, selected from the brain map:

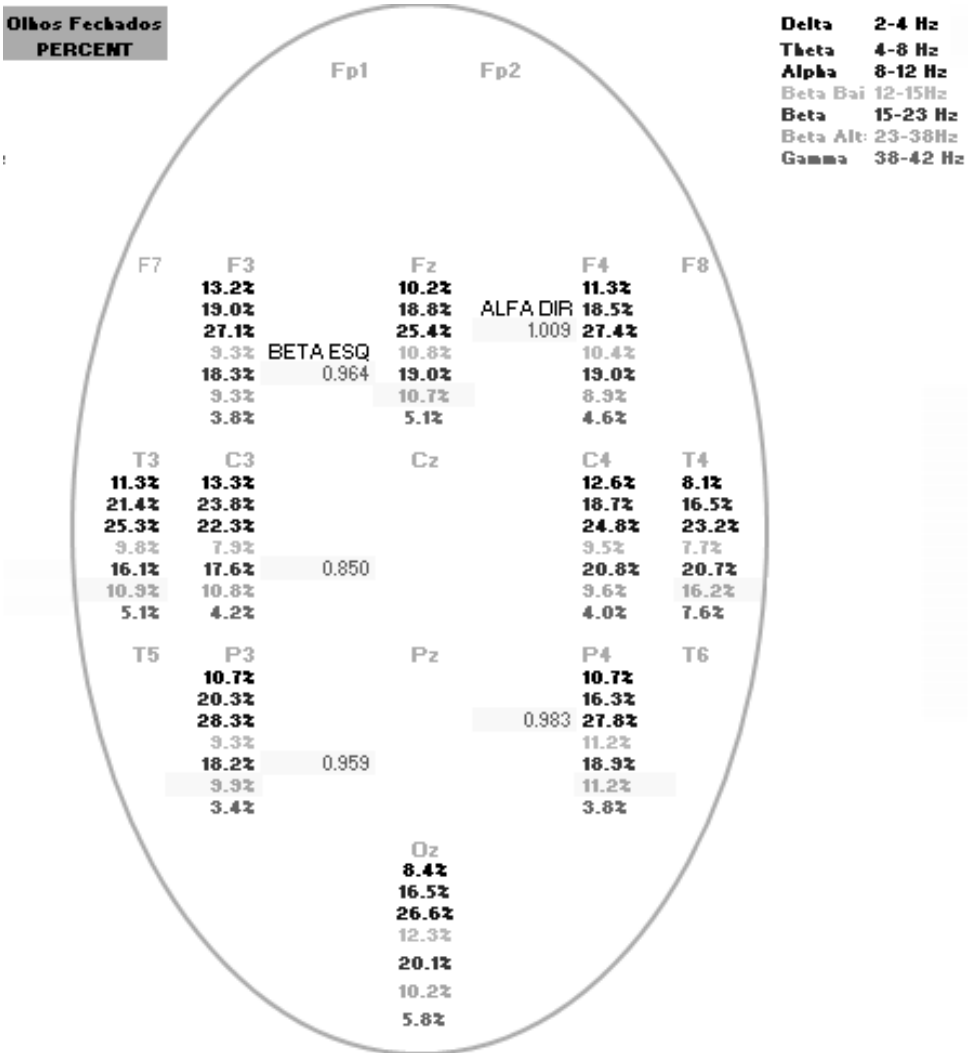

Figure 2. Main trends of the subject's brain map before the experiment.

This image comprises a selection of the subject's EEG (relative power in frequency bands showing the percentages in the different bands summing 100%), while she was sitting passively, with closed eyes. Each frequency band is correlated with a color, as presented in the legend that is found in the upper part of the image (frequency bands were obtained through Fast Fourier Transform). Dark blue represents "Alpha;" red and orange relate to the two bands of "Beta," respectively "desirable" (Beta1) and "undesirable" (Beta 3).

The mini-QEEG of the subject is characterized by a mild frontal asymmetry to the right, with predominance of slow and medium wave activation (Delta, Theta and Alpha) on the left. In accordance with what we said before, it is possible to infer that the findings correlate with the persistent negative emotions and low cognitive activation experienced by the subject, although not necessarily to MDD. Our protocol responds directly to this profile in that it focuses on the inversion of this asymmetry, while seeking a right predominance of Alpha and a Beta predominance to the left, limited by the conditional reinforcement for Beta 3 inhibition.

Subject Evolution

Figure 3 (see below) presents the 'trend graph' of brain performance evolution during the course of the 10 training session's trial. This graph is based on data representing the average results of all training time in a condition (ten conditions of five minutes); the graph line "Percentage of Global Success" relates to the percentage of the time in which all three dimensions of the protocol had been reached simultaneously and held for at least one half second.

Considering all 10 sessions, the EEG performance trend of the subject can be defined as "moderate" and "consistent", although certain intra and inter-session oscillations are observed. As apparent at the last portion of the graph, which shows the last register of the training protocol ("all the conditions passing"), the subject evolved from 15% success at the beginning of the protocol to 26% success (in the last session). Unfortunately, these oscillations generate very high standard deviations of the metric (7.8), which raise a note of caution toward any effusive reaction concerning such results. We hypothesize that these oscillations are mainly related to the necessity of a greater number of sessions for the long-term fixation of the recently learned brain activation patterns.

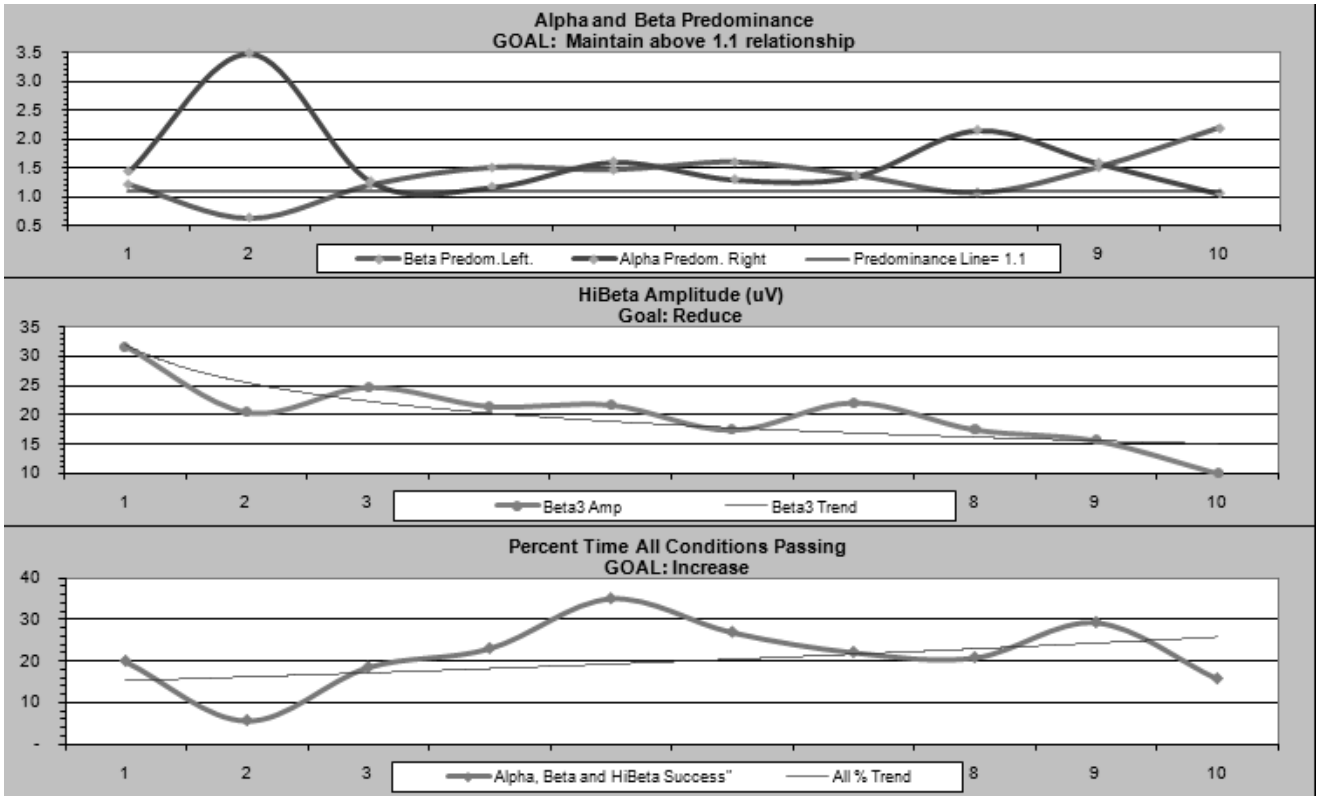

Figure 3. Evolution of the capacity to achieve the training demands after 10 sessions.

Date:	21-Jul-09	31-Jul	7-Aug	11-Aug	14-Aug	18-Aug	21-Aug	25-Aug	28-Aug	1-Sep	4-Sep		
Intensity Rating:	0=Never, 1=Light/Rare, 4=Moderate/Half the Time, 7=Severe/Continuous												
Symptom	**Rating**												
Anxious	7	3	2	3	1	2	2	3	3	2	2	1.555	
Irritable	6	2	3	3	2	2	3	2	2	2	2	1.206	
Negative Thinking	6	5	3	4	1	2	1	2	2	3	3	1.578	
Obsessive Thinking	6	2	2	2	2	1	1	2	2	2	1	1.375	
Agitated	5	3	3	3	2	1	1	2	2	2	3	1.128	
Cry Easily	5	2	2	2	2	3	2	3	2	3	2	0.934	
Difficulty Falling Asleep	5	1	2	3	3	2	2	3	2	3	2	1.036	
	5.71	Ave Pre		Averaged Reduction:			3.57			Ave Post	2.14	1.26	Ave.SD
	0.756	SD Pre								SD Post	0.690		

Figure 4. Self-evaluative questionnaire that we developed and that was answered by the subject. Through the application of this method, the subject answers to several questions regarding his psychological and psychiatric state, subsequent to which a macro select the most prominent answers, in order to aid the process of understanding the full complexity of the subject's condition, regardless of its occasional departure from well-established psychiatric disorders.

In any case, this data must be considered in association with the subject's self assessment, which took place during all the training period, as seen below, in figure 4.

In the initial evaluation, the subject revealed considerable mental suffering, relating the most intense suffering of: 1. Anxiety, 2. Irritation, 3. Negative thoughts, 4. Obsessive thoughts, 5. Agitation, 6. Frequent crying, 7. Difficulties falling asleep. When initiating the experiment, the average intensity of these complaints, on a 0-7 scale was 5.71. When completing the ten sessions, the average reported by the subject was 2.14, a 43% reduction.

In a generalized manner, the data suggests an improvement in the subject's emotional profile, both in terms of her capacity to answer to the demands of the new protocol and therefore to break with electrophysiological patterns typical of low mood experiences and in terms of her declared self-perception. However, it is important to consider that the most significant improvements were perceived in the first few training sessions, which may point to the potential effect of her expectation (placebo).

Considering this possibility, we established telephone contact with the subject after one month, with the intention to qualitatively investigate her perception in relation to the complaints initially presented. This contact confirmed the settling of the improvement trend inferred at experiment's end.

Conclusion

This study presents an innovation on the field of neurofeedback treatment of depression, represented by a new training protocol that integrates different brain demands. The protocol seems to be advantageous, both in practical and theoretical terms. Beginning with a demonstration concerning the adequacy in attending to EEG demands that are emphasized in the relevant literature, we tested it in two ways: assessing whether the protocol addresses achievable electrophysiological demands of a depressive patient and evaluating whether noticeable subjective evolution could be obtained using this protocol.

Encouraging results have been found in relation to the two aspects through which the protocol was submitted to testing, suggesting that the development of more studies in this scope is worthwhile, in order to overcome the limitations evident in our clinical experiment. Also, the potential viability of the new protocol in relation to cases of deep depression with EEGs showing more sharp asymmetries to the right is an avenue of further research.

We also consider that the use of this approach could well be integrated to others (medication, psychotherapy), with the advantage of enhancing traditional interventions. In light of the fast development of the use of the EEG for diagnosis and treatment, we believe that this association will become increasingly popular in the near future, establishing itself as one of the canons in the treatment of depression.

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