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DIFFERENTIATING A NETWORK OF EXECUTIVE ATTENTION: LORETA NEUROFEEDBACK IN ANTERIOR CINGULATE AND DORSOLATERAL PREFRONTAL CORTICES

Rex Cannon, Marco Congedo, Joel Lubar, Teresa Hutchens

ABSTRACT

Introduction:

This study examines the effect of LORETA (low-Resolution Electromagnetic Tomography) neurofeedback training (LNFB) in three regions of interest; a 7 voxel cluster of neurons in the cognitive division of the anterior cingulate gyrus (ACC), a three-voxel cluster of neurons in the left dorsolateral prefrontal cortex (LPFC) and a five-voxel cluster of neurons in the right dorsolateral prefrontal cortex (RPFC). We trained participants to increase 14-18 Hz activity in each of the regions of interest (ROI) over twenty sessions.

Methods:

This study was conducted with fourteen non-clinical students with a mean age of 22. We utilized electrophysiological measurements and subtests of the WAIS-III for pre and post measures to assess the influence of this training protocol.

Results:

The data indicate significant differences in activation patterns within these regions and throughout the cortex. More specifically the data indicate that the AC shares a significant association with the RPFC and LPFC; however, each region exhibits different cortical effects when trained exclusively.

Discussion:

Rather then increasing current density selectively in the training region and in the trained frequency, LNFB seems to enhance the functioning of a network of cortical functional units physiologically related to the training region, involving several frequencies possibly associated with the functioning of the network. The AC and RPFC appear to influence a specific frontal circuit in the trained frequency as compared to the LPFC. The AC initiates regions that do not appear to be affected by either of the other ROIs. The data offer further support to the moderation of the central executive by the dorsolateral prefrontal cortex, particularly in the right hemisphere and AC; as a consequence of the neurofeedback training we observed significant improvements in both working memory and processing speed.

1: Introduction

The anterior cingulate gyrus (AC) has been the topic of an enormous amount of research in recent years and continues to be a focus of concentrated study. Experiments report activation of the AC in attentional, cognitive, mnemonic and emotional processes (Bench, Frith, Graby, Friston, Paulesu, Frackowiak, & Dolant, 1993; Carr, 1992; Duncan & Owen, 2000; Fazio, Perani, Gilardi, Colombo, Cappa, & Vallar, 1992; Garavan, Ross and Stein, 1999; Heyder, Suchan, & Daum, 2004; Kondo, Morishita, Osaka, Osaka, Fukuyama, Shibasaki, 2003; Markela-Lerenc et *al*., 2004; Ortuño, Ojeda, Arbizu, Lopez, Marti-Climent, Peñuelas, & Cervera, 2001; Pardo, Pardo, Janer, & Raichle, 1990; Posner and Peterson, 1990). Kane and Engle (2002, 2003) suggest that executive attention is moderated by the prefrontal cortices, with an emphasis on the role of the dorsolateral prefrontal cortices as being primary to working memory (WM) to maintain information in an active, easily available condition. Saykin and colleagues (1992) propose the material specific or ipsilateral deficit model, which asserts that memory function corresponds to known cerebral function, viz., that the left hemisphere, particularly in the frontal and temporal regions, regulates verbal memory with similar regions in the right regulating visuospatial memory (according to language dominance).

Several theories relating to the role of anterior cingulate cortex (AC) in attentional and executive processes have been suggested without clarity of the interactions between the AC and prefrontal cortices (PFC), despite the probability that attentional processes are the most investigated function of the AC (Pardo, Pardo, Janer, & Raichle, 1990; Bench, Frith, Graby, Friston, Paulesu, et al, 1993; Posner & Petersen, 1990). Positron Emission Tomography (PET) studies report bilateral metabolic reductions in the hippocampal formation, thalamus, AC and frontal basal cortex in persons suffering from the amnesic effects of post-ischemic hypoxia, which offers support to the contribution of the AC in a network involving memory (Fazio, Perani, Gilardi, Colombo, Cappa, & Vallar, 1992).

One prominent theory proposes that the AC detects the need for executive control and signals the PFC to execute the control (Markela-Lerenc et *al*., 2004); similarly, researchers propose that the AC is in effect a gating mechanism between the cortex and subcortical regions (Pizzagalli, et al 2003). These two ideas are supported given that the AC receives inputs from regions involved in memory, emotion, reward, nociception, and autonomic functioning along with other subcortical nuclei (Bush, Luu and Posner, 2000). Studies report persons with lesions to the frontal lobes or removal of frontal regions may continue to perform within normal range on standardized intelligence tests but also do better on perceptual or memory tasks that persons with left or right temporal lesions, and persons with frontal lobe lesions are responsive to external stimuli; however, are distracted by them, yet have difficulty utilizing these stimuli as cues for behavioral regulation (Milner, 1995). If we were to combine these theoretical concepts, it is reasonable to infer that the AC maintains a presidential role in executive attention; however, this attentive process is governed in the right hemisphere, mainly in the right dorsolateral prefrontal cortex (RPFC), while the LPFC dorsolateral left prefrontal cortex is more the governing force of working memory and reclamation memory processes, given that many of the regions active during working memory and episodic retrieval are also active during other types of tasks including visual attention (Cabeza, et al, 2003). The AC is divided into cognitive and affective divisions, and research indicates that persons with attention-deficit-hyperactivity disorder fail to activate the cognitive division during Stroop interference tasks. Similarly, research suggests the cognitive division of the AC is activated during divided attention tasks and the affective division is decreased in activation during cognitive tasks and vice versa (Bush, et al 2000). Thus we would conclude that there is an underlying network involving DLPFC, AC and numerous other regions in which the AC deciphers, directs and blends memory and attention to form and maintain executive attention.

Neurofeedback techniques have been utilized in clinical and research settings for treatment of neurological and psychiatric disorders (Sterman, 2000, 2001; Lubar and Lubar, 1999; Peniston and Kulkosky, 1989, 1990, 1991), and continue to be a focal point for development of possible treatments for psychological disorders as well as discovery of functional processes. A recent fMRI study reports neurofeedback techniques initiating blood oxygenated level dependent (BOLD) changes in the AC, caudate and substantia nigra in AD/HD children (Levesque, Beauregard & Mensour, 2006). LORETA neurofeedback (LNFB) is a recent advancement in the neurofeedback method (Congedo, Lubar and Joffe, 2004) offering the possibility to influence regions deep in the medial temporal lobes, limbic regions and regions at the base of the brain, such as the insular cortex, parahippocampal, lingual, fusiform, and orbital-frontal gyri, to which the contribution to surface EEG is poor. LORETA (Pascual-Marqui, 1995, 1999; Pascual-Marqui, Michel, & Lehmann, 1994; Pascual-Marqui, 2002 ; Pascual-Marqui et *al*., 2002, 2002a, 2002b) is an inverse solution estimating cortical electric current density originating from scalp measurements, utilizing realistic electrode coordinates (Towle et *al*., 1993) for a three-concentric-shell spherical head model co-registered on a standardized MRI atlas (Talairach, & Tournoux, 1988) approximate anatomical labeling of the neo-cortical volume is possible (Lancaster et *al*., 1997, 2000).

In this study we use the three-shell concentric spherical head model implementation made available from the Key Institute for Brain-Mind Research, Zurich, Switzerland. In this implementation, the current density is mapped for 2394 voxels of dimension 7x7x7 mm covering the entire neocortex plus the AC and hippocampus. In conventional neurofeedback, electroencephalographic (EEG) activity is recorded at a particular scalp location. The physiological measurements are extrapolated from the signal and converted into auditory stimuli or visual objects that animatedly co-vary with the magnitude of a specified frequency or frequency band-pass region. Similarly, LNFB correlates the physiological signal with a continuous feedback signal; however, the physiological signal is defined as the current density in a specified region of training (ROT). This allows the continuous feedback signal to become a function of the intracranial current density and to covary with it. The advantage over traditional neurofeedback is increased specificity of the training.

This study is part of an ongoing effort to investigate the simultaneous changes that occur in several regions of the cortex as a consequence of either traditional or LORETA neurofeedback training (Cannon, et. al., 2006, 2007; Congedo, 2003, 2006; Congedo, Lubar & Joffe, 2004). We sought to define the correlation structure of cortical regions directly involved in the self-regulation of the electrical activity in the AC, LPFC, RPFC and the differences between activation patterns extracted in six other regions; moreover, we examine specific frequency changes resulting from increasing and maintaining 14 – 18 Hz in the ROT. Particularly; our study investigates the efficacy of

LNFB training within each of the regions of training (ROT) (see table 1) and the respective effects in these connected regions of interest (ROI) (see table 2). The effects of the training were assessed by means of a number of electrophysiological and statistical measures; also the efficacy of the training was assessed by means of pre-post training psychometric testing using subtests of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III).

Table 1: Regions of Neurofeedback Training (ROTs) in the cortex, the number of voxels assigned to the region by LORETA, the X, Y, Z Talairach Coordinates and the region of the brain.

Region of Training (ROT)	*Talairach (voxel) X, Y, Z Coordinates*	*Brodmann Area / anatomical label*
AC	(-3 31 22) (-3 24 29) (-10 31 29) (-3 31 29) (4 31 29) (-3 38 29) (-3 31 36)	BA 32, anterior cingulate, limbic lobe.
LPFC	(-38 31 36) (-38 31 43) (-31 31 43)	BA 8, middle frontal gyrus, frontal lobe
RPFC	(39 31 36) (39 24 36) (39 24 43) (32 31 43) (39 31 43)	BA 8, middle frontal gyrus, frontal lobe

Table 2: Regions of interest (ROIs) in the cortex, the number of voxels assigned to the region by LORETA, the X, Y, Z Talairach Coordinates and the region of the brain.

ROI	# of Voxels[3]	X, Y, Z Talairach coordinates	Brain Region
Anterior Cingulate Gyrus	7	(-3, 31, 22) (-3, 24, 29) (-10, 31, 29)(-3, 31, 29) (-4, 31, 29) (-3, 38, 29)(-3, 31, 26)	Brodmann area 32, anterior cingulate gyrus, limbic lobe
Left Dorsolateral Prefrontal Cortex	3	(-38, 31, 36) (-38, 31, 43) (-31, 31, 43)	Brodmann area 8, middle frontal gyrus, frontal lobe
Right Dorsolateral Prefrontal cortex	4	(39 31 36) (39 24 36) (39 24 43) (32 31 43) (39 31 43)	Brodmann area 8, middle frontal gyrus, frontal lobe

Right Post-central gyrus	5	(46, -25, 43) (53, -25, 43) (60, -25, 43) (53, -18, 43) (53, -25, 50)	Brodmann area 3, post-central gyrus, parietal lobe
Left supramarginal gyrus	5	(-59, -53, 15) (-59, -60, 22) (-59, -53, 22) (-59, -46, 22) (-59, -53, 29)	Brodmann area 40, supramarginal gyrus, temporal lobe
Right supramarginal gyrus	6	(60, -53, 15) (60, -60, 22) (53, -53, 22) (60, -53, 22) (60, -46, 22) (60, -53, 29)	Brodmann area 40, supramarginal gyrus, temporal lobe
Cuneus	7	(-3, -67, 22) (-3, -74, 29) (-10, -67, 29) (-3, -67, 29) (4, -67, 29) (-3, -60, 29)(-3, -67, 36)	Brodmann area 7, Cuneus, occipital lobe

2: Methods

2:1 Participants

This study was accomplished with fourteen participants, six male and eight female non-clinical students, with a mean age 21.21, standard deviation of 2.39 and range 18 - 26. Thirteen of the participants were right handed and one was ambidextrous. The group receiving LNFB training in the AC consisted of eight participants, the groups receiving LNFB training in the RPFC and LPFC contained three participants each. All participants read, signed and agreed to an informed consent to protocol approved by the University of Tennessee Institutional Review Board. Participants received extra course credit for participating in this study. Exclusionary criteria for participation included previous head trauma, history of seizures, recent drug or alcohol use and any previous psychiatric diagnosis.

2:2 Procedures

Participants were prepared for EEG recording using a measure of the distance between the nasion and inion to determine the appropriate cap size for recording (Electrocap, Inc; Blom & Anneveldt, 1982). The head was measured and marked prior to each session to maintain consistency. The ears and forehead were cleaned for recording with a mild abrasive gel to remove any oil and dirt from the skin. After fitting the caps, each electrode site was injected with electrogel and prepared so that impedances between individual electrodes and each ear were < 6 KΩ. The LNFB training was conducted using the 19-leads of the standard international 10/20 system (FP1, FP2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1 and O2). The data was collected and stored with a band-pass set at 0.5–64.0 Hz at a rate of 256 samples per second. All recordings and sessions were carried out in a comfortably lit, sound attenuated room in the Neuropsychology and Brain Research Laboratory at the University of Tennessee, Knoxville. Lighting and temperature were held constant for the duration of the experiment. Each session required approximately forty minutes to complete.

2:3 Neurofeedback Protocol

Twenty LNFB training sessions composed of four, four-minute rounds were conducted three times per week. Following standard protocol (Congedo, Lubar and Joffe, 2004; Cannon, et al., 2007) we designed to improve attentional processes by training individuals to increase 14 -18 Hz (low-beta) power activity in one of three ROT (see table 1); a three-voxel cluster of neurons in the left dorsolateral prefrontal cortex, a five voxel cluster of neurons in the right dorsolateral prefrontal cortex and compared them to a seven-voxel cluster of neurons in the cognitive division of the AC. In a preliminary session, the participants were instructed to control tongue and eye movements, eye-blinks, and muscle activity from forehead, neck, and jaws. This enabled the subjects to minimize the production of extra-cranial artifacts (EMG, EOG, etc.) during the sessions. At the end of the preliminary session, they were informed of the inhibitory and reward aspects of the training. Standardized thresholds were then set and maintained for each participant.

Table 3: The inhibit and reward parameters for LNFB training

(A)	Electro-oculogram (EOG) < 15.0 (Microvolts) Decrease 1 – 3 Hz activity in a linear combination of six frontal channels, FP1, FP2, F3, F4, F7, F8	SUPPRESS
(B)	Electromyogram (EMG) < 6.0 (Microvolts) Decrease 35 – 55 Hz activity in a linear combination of six temporal and occipital channels, T3, T4, T5, T6, O1, and O2	SUPPRESS
(C)	Region of Training (ROT) > 5.0 (Current Density) Increase current source density (14 – 18 Hz) in the ROI.	ENHANCE

Following Congedo, Lubar and Joffe (2004) the participants were provided visual and auditory feedback and points were achieved when they were able to simultaneously maintain all conditions specified in table 3 (A *and* B *and* C). Maintaining all conditions for 0.75 seconds achieved one point. The auditory stimuli provided both positive and negative reinforcement, an unpleasant splat sound when the conditions were not met and a pleasant tone when they were. Similarly, the visual stimuli were activated when the criteria were being met, e.g., a car or a spaceship driving faster and straighter. Alternatively, a slower car, driving in the wrong lane or the spaceship flying slow and crooked occurred when the criteria were not being met. The score for meeting the criteria was also seen by the participants in a small window of the game screen.

2:4 Data Collection

In contrast with studies utilizing traditional neurofeedback, the whole-head EEG data was continuously stored during the sessions. In addition, the participants in this study provided a written record of their experience, strategies, and mental processes employed to obtain points for each session during this training.

2:5 Data Pre-Processing

All EEG data were processed with particular attention given to the frontal and temporal leads. All episodic eye blinks, eye movements, teeth clenching, jaw tension, body movements and possible EKG (Electrocardiogram) were removed from the EEG stream. Fourier cross-spectral matrices were computed and averaged over 75% overlapping four-second artifact-free epochs, which resulted in one cross-spectral matrix for each subject and for each discrete frequency. These cross-spectral matrices constitute the input for LORETA estimation in the frequency domain.

2:6 Psychometric Pre Training Measures

We administered the Weschler Adult Intelligence Scale – Third Edition (WAIS-III) for a pre-training measure. Table 4 shows select mean pre training WAIS-III scores.

Table 4 contains the group averages of pre training WAIS-III scores. The table contains the WMI, PSI and FSIQ scores and standard deviation for each.

Group	*WMI*	*SD*	*PSI*	*SD*	*FSIQ*	*SD*
AC	117.5	16.44	106.62	11.13	124.25	6.79
RPFC	96.67	8.33	114.00	9.85	111.33	1.53
LPFC	97.67	4.04	111.33	2.52	106.00	8.72

For post training measures we selected the Working Memory Index (WMI) and Processing Speed Index (PSI) scores. The WMI score consists of the sum of scaled scores in the Arithmetic (A), Digit Span (DS) and Letter-number sequencing (LN) subtests. The PSI score consists of the sum of scaled scores in Digit-symbol Coding (CD) and Symbol Search (SS). We used these combinations of subtest scores following indication of Sattler (2001).

2:7 Data Statistical Analysis

In this study, we focus on seven ROIs, of which one is the *active ROT* (Table 1) and the other six, the *secondary ROIs*, have been found to be functionally associated to it. Table 2 lists the name of the ROIs, the number of voxels composing it; the Talairach coordinates of all voxels within the ROI and its Brodmann area/anatomical labeling. After averaging across the four rounds within each session for each ROT, we conducted a Pearson partial correlation analysis to assess a linear upward or downward trend of the current density changes in the seven ROIs according to ROT, using data in the training frequency range (14 - 18Hz). This stage was conceived to individuate those ROIs in which current density amplitude tends to increase (positive correlation) or decrease (negative correlation) as a function of the neurofeedback learning process in the region of training (ROT). We utilized the partial procedure in order to control for the effects of volume conduction, that is, we assessed the correlation between any two regions taking into account the influence of the remaining five regions. Threshold of significance for the correlation coefficients r was set to abs(r) = 0.01. Similarly, we averaged the mean current density and plotted the learning curves exhibited in each of the anterior ROIs as a result of training in the three anterior ROTs. The analysis was carried out for the following frequencies band-pass regions: Delta (0.5 – 3.5 Hz); Theta (3.5 – 8.0 Hz); Alpha 1 (8.0 – 10.0 Hz); Alpha 2 (10.0 – 12.0 Hz); Beta (12.0 – 32.0 Hz); Trained Frequency (TF 14 – 18 Hz). We also implemented the well known False Discovery Rate (FDR) multiple testing procedure of Benjamini and Hochberg (1997) for testing the probability values obtained in the partial correlation analyses. We also analyzed the pre and post psychometric scores using an ANOVA. This analysis tests whether the spatial-specific training of low-beta activity in the given ROT results in a positive influence in cognitive performance related to attention and executive processes in normal subjects.

3: Results:

3:1 Correlations Between ROIs:

Tables 5 through 10 show the results for the partial correlation analysis in the trained frequency (14 – 18 Hz) and the degree to which neuronal populations in the extracted anterior regions of training share an association with each other per each frequency band, controlling for each other respectively. Contained in the table from left to right are the ROI, the ROT, *rho* value and the probability of *rho*. Table 1 shows the results for the trained frequency. We will address these results by frequency in the following subsections.

3:1:1 Trained Frequency Bands

Figure 1 and table 5 show the results for the trained frequency. The AC shows the only significant positive relationship with the cuneus in the trained frequency, which possibly indicates the communication between anterior and posterior regions of the cingulate gyrus through thalamic regions. The (q) reported by the FDR procedure for (14 – 18 Hz) indicates thresholds of significance: AC = (0.016); LPFC = (0.062); RPFC = (-0.562). The AC shares a positive relationship with the Cuneus, LPFC, RPCG and RSMG and shares no apparent relationship with either the RPFC or LSMG in the trained frequency. Contrasting the training in the AC, the LPFC shows significant negative relationships with the RPCG and Cuneus, and positive relationships with the AC and RPFC; and shows no relationship with either the LSMG or RSMG in the trained frequency. The RPFC shows a different pattern of association as compared to the AC or

LPFC. The results indicate positive significant relationships with all regions in the trained frequency except for the RSMG and cuneus; the RPFC is negatively associated with the cuneus in the trained frequency. The AC shows significant associations with the RPCG and LPFC. This is possibly attributed to the encoding of somatosensory and attentional processes to memory for use in the training, i.e., preparing information to be used in a goal directed function. Of particular note, is the AC not having an association with the RPFC in the trained frequency; this is possibly attributed to the RPFC being influenced by regions involved in attentive processes as opposed to WM tasks. The LPFC, on the other hand is associated with only the AC and RPFC in the trained frequency. This offers insight into the HERA model; in that, the LPFC is involved in the encoding and retrieval aspects of memory and perhaps instrumental in most memory processes; alternatively the RPFC is more specific to attention. For memory to be useful in cognitive and executive processes, it demands attention, in the same fashion that the learning of external, novel tasks demands attention and this integration of processes requires close cooperation between the AC, LPFC and RPFC. The RPFC is positively associated with the AC, LPFC, LSMG, and RPCG in the trained frequency. This pattern offers evidence for the role of the RPFC in attention and is a plausible demonstration of the RPFC attending to somatosensory information, language and memory processes and aiding the AC in directing information to the LPFC and associated limbic regions for commitment to memory stores. The RPFC shares a negative association with the cuneus, which is a possible example of the direct communication between the anterior and posterior cingulate in visual and mnemonic processing. The linear increase in these regions appears to coincide with the increase in the ROT.

3:1:2 Alpha 1 Frequency Bands

Figure 2 and table 6 show the results for the partial correlation analysis for the alpha 1 frequency. The (q) reported by the FDR procedure for (8 – 10 Hz) indicates thresholds of significance: AC = (-0.059); LPFC = (-0.103); RPFC = (-0.377). The AC shares significant positive associations with the cuneus and LPFC in this frequency, and shares negative associations with the RPCG and RSMG. The LPFC shares positive relationships with the AC, RPFC, and LSMG in this frequency and a negative relationship with RPCG. The RPFC shows positive effects with the AC, LSMG and RPCG and negative effects with the LPFC and cuneus in this frequency. Alpha 1 is postulated to be involved mainly in attentional processes and to play an indirect role in memory. The relationship between the AC and cuneus may describe the evaluative and decision making and goal direction of sensory information. The LPFC may be involved in combination with the AC, LSMG and anterior regions in the encoding of information from regional processing. The RPFC, AC and RPCG are plausibly directly responsible for attentional processes as well as processing information from the LSMG for evaluation and attendance to language for verbalization processes.

3:1:3 Alpha 2 Frequency Bands

Figure 3 and table 7 show the results for the alpha 2 frequency. The (q) reported by the FDR procedure for (10 – 12 Hz) indicates thresholds of significance: AC = (-0.059); LPFC = (-0.184); RPFC = (-0.061). The AC shows positive relationships with the cuneus and LPFC. The LPFC shows significant positive relationships with the AC, RPFC and LSMG, and a negative relationship with the cuneus. The RPFC shows significant positive relationships with the AC and RPCG and a negative relationship with the cuneus.

The relationship between AC and cuneus maintains in this frequency and may reflect the encoding and retrieval processes relating to visual information processing and evaluative processes of performance, game, and attention to internal state. The LPFC, along with the AC, LSMG, and RPFC may suggest a role or primary encoding. The RPFC, AC and RPCG persist in this frequency; again it is plausible this is a primary right hemispheric attentional process.

3:1:4 Beta Frequency Bands

Figure 4 and table 8 show the results for the beta frequency. The (q) reported by the FDR procedure for (12 – 32 Hz) indicates thresholds of significance: AC = (0.002); LPFC = (0.017); RPFC = (0.061). The AC shows significant positive relationships with the LPFC, RPCG, and cuneus, while showing negative relationships with the RSMG and LSMG. The LPFC shows positive relationships with the AC, cuneus, and LSMG and a negative relationship with the RPCG. The RPFC again shows a positive relationship with the AC and RPFC with no other effects for the overall beta frequency. The relationship between the AC, cuneus and RPCG is perhaps the executive task for the AC, i.e., the integration of sensory, visual and thalamic information and involving the LPFC in memory of this code without aid from parietal regions. The LPFC, LSMG, cuneus and AC may again reflect the faster processes required for encoding and committing this information to memory stores involving other limbic structures. The RPFC shows only effects for the RPCG and AC – which again offers insight into the vital relationship of these regions in higher attentional processing, possible verbalization processes and the sate of the individual in space (attention to muscle, eye movements, and inhibits).

3:1:5 Theta Frequency Bands

Figure 5 and table 9 show the results for the theta frequency. The (q) reported by the FDR procedure for (14 – 18 Hz) indicates thresholds of significance: AC = (0.038); LPFC = (0.038); RPFC = (0.035). The AC shows only a positive relationship with the LPFC and a negative relationship with the RPCG in this frequency. The LPFC shows positive relationships with the AC and RSMG and a negative relationship with the RPCG. The RPFC shows only positive relationships with the RPFC and RPCG. The theta frequency appears to exact less global effects as the other frequencies. The AC and LPFC may be involved in encoding processes. The LPFC, AC and RSMG may be involved in encoding spatial orientation relating to the internal and external state, while the RPFC, AC and RPCG are possibly involved in the encoding and development of attentional processes.

3:1:6 Delta Frequency Bands

Figure 6 and table 10 show the results for the delta frequency. The (q) reported by the FDR procedure for (14 – 18 Hz) indicates thresholds of significance: AC = (0.027); LPFC = (-0.081); RPFC = (-0.081). The AC shows a positive relationship with the LPFC and a negative relationship with the RSMG. The LPFC shows positive relationships with the AC and RSMG and a negative relationship with the RPCG. The RPFC shows positive relationships with the AC, RPCG and LSMG and a negative relationship with the cuneus. The delta frequency is suggested to be intricately involved in long range communications between regions. There are strong associations between the LPFC and AC that appear to be reciprocal, while the AC does not communicate with posterior regions in this frequency, the LPFC does. This may suggest encoding and monitoring of information for importance for encoding. The RPFC continues to show the AC and RPCG along with the

LSMG in this frequency. This is suggested to reflect an attentional process and possible integration of language for verbalization processes.

3:1:7 Learning Curves in Anterior Regions

Figures 7, 8 and 9 show the linear increase in current density over sessions, i.e. the learning effect for each ROT and the effects of LNFB in the other ROT on that region. Figure 7 shows the linear increase for the AC as a result of LNFB training. This learning effect is significant. Training in the LPFC and RPFC appear to influence activity increase in this cluster of neurons within the AC at a higher degree than training in the AC. Training in the AC produces effects differently than training in either of the dorsolateral prefrontal regions. This pattern is similar in Figures 8 and 9 for the LPFC and RPFC respectively.

One partial explanation for the synchronous increase in the anterior ROIs for each ROT is the HERA (hemispheric encoding/retrieval asymmetry) model (Tulving et al., 1994b; Buckner, 1996; Habib, et al, 2003) in which the idea that encoding and retrieval processes involving episodic and semantic memory initiate activity in the frontal lobes asymmetrically in idiosyncratic fashion. This is interpreted as the HERA model of the involvement of the frontal lobes in encoding and retrieval, which posits that the left frontal lobes are differentially more involved in the retrieval of general knowledge (semantic memory information); and encoding of novel aspects of incoming information into episodic memory, including information retrieved from semantic memory; while the right frontal lobes are more involved in episodic memory retrieval. Cabeza, et al (2003) suggests that similar regions are commonly active during working memory, retrieval and encoding tasks, and goes further to explain that other types of tasks such as visual attention also illicit activity in these regions. This activation pattern is affirmed in this study; however, we would posit that synchronous increase in activation does not infer synchronous function.

Table 5: Partial correlation analysis for the trained frequency (14 – 18 Hz). In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.412	.000
LPFC	0.475	.000
LSMG	-0.003	.936
RPCG	0.137	.000
RPFC	0.016	.613
RSMG	-0.162	.000
	LPFC	
Cun	-0.142	.007
AC	0.784	.000
LSMG	-0.083	.119
RPCG	-0.296	.000
RPFC	0.128	.016
RSMG	0.062	.245
	RPFC	
Cun	-0.562	.000
AC	0.233	.000
LPFC	0.119	.025
LSMG	0.276	.000
RPCG	0.723	.000
RSMG	0.229	.092

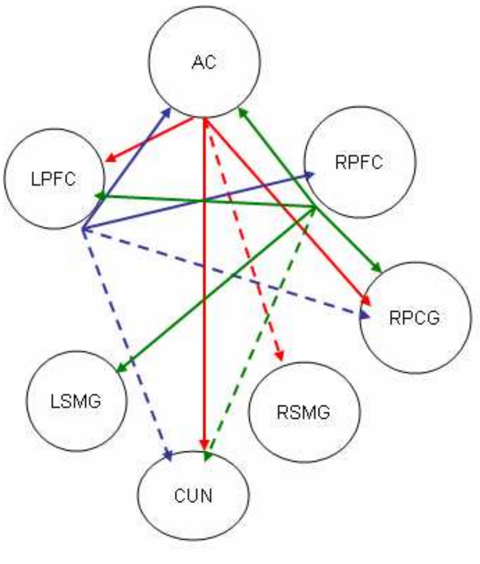

Figure 1: Schematic of partial correlations initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. The AC appears to share a positive association with the cuneus, RPCG and LPFC and a negative association with the RSMG. There was no effect for RPFC and LSMG with the AC. The LPFC shares a significant positive association with the AC,

RPFC and RPCG and a negative association with the cuneus; the parietal regions had non-significant values. The RPFC, on the other hand, shares a significant positive relationship with all regions except for the cuneus; this relationship is negative at significant levels and the RPFC shows non-significant effect for the RSMG.

Table 6 Partial correlation analysis for the alpha 1 frequency (8 – 10 Hz) relative to training (14 – 18 Hz) for each ROT. In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.263	.001
LPFC	0.208	.009
LSMG	0.120	.137
RPCG	-0.101	.212
RPFC	0.079	.329
RSMG	-0.059	.465
	LPFC	
Cun	-0.103	.454
AC	0.640	.000
LSMG	0.299	.027
RPCG	0.324	.016
RPFC	0.356	.008
RSMG	-0.270	.046
	RPFC	
Cun	-0.513	.000
AC	0.747	.000
LPFC	-0.377	.005
LSMG	0.469	.000
RPCG	0.796	.000
RSMG	0.229	.092

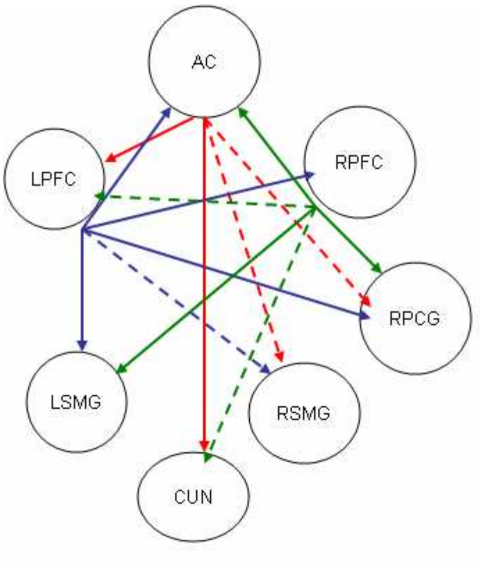

Figure 2 Schematic of partial correlations initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. schematic of partial correlations for the alpha 1 frequency (8 – 10 Hz). Training in the AC produces strong positive associations between the AC and LPFC in this frequency, and produces strong negative associations between the AC and RPCG and RSMG. The LPFC appears to have a more influential role in this frequency, sharing positive relationships with the AC, LSMG, RPFC and RPCG and a negative relationship with the RSMG. The RPFC shares positive relationships with the AC, RPCG and LSMG, while sharing negative associations with the LPFC and cuneus.

Table 7 Partial correlation analysis for the alpha 2 frequency (10 – 12 Hz) relative to training in 14 – 18 Hz for each ROT. In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.263	.001
LPFC	0.208	.009
LSMG	0.120	.137
RPCG	-0.101	.212
RPFC	0.079	.329
RSMG	-0.059	.465
	LPFC	
Cun	-0.415	.002
AC	0.383	.004
LSMG	0.450	.001
RPCG	-0.184	.180
RPFC	0.605	.000
RSMG	0.158	.250
	RPFC	
Cun	-0.522	.000
AC	0.631	.000
LPFC	-0.061	.658
LSMG	0.195	.153
RPCG	0.652	.000
RSMG	0.233	.087

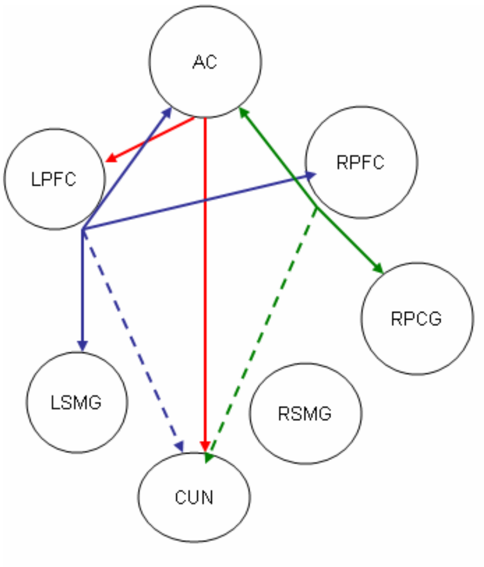

Figure 3 Schematic of partial correlations for the alpha 2 frequency (10 – 12 Hz) initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. schematic for the partial correlations in the alpha 2 frequency relative to training 14 – 18 Hz in each respective ROT. The AC shares significant positive relationships with the LPFC and cuneus in this frequency. The LPFC shares significant positive relationships with the AC, RPFC and LSMG, while showing a negative relationship with the cuneus. The RPFC also indicates a negative relationship with the cuneus and positive relationships with the AC and RPCG.

Table 8 Partial correlation analysis for the beta frequency (12 – 32 Hz) relative to training 14 – 18 Hz in each ROT. In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.382	.000
LPFC	0.687	.000
LSMG	-0.135	.001
RPCG	0.256	.000
RPFC	0.002	.955
RSMG	-0.224	.000
	LPFC	
Cun	0.265	.000
AC	0.764	.000
LSMG	0.383	.000
RPCG	-0.292	.000
RPFC	0.069	.292
RSMG	0.017	.800
	RPFC	
Cun	-0.087	.185
AC	0.607	.000
LPFC	0.061	.351
LSMG	-0.005	.938
RPCG	0.249	.000
RSMG	-0.090	.168

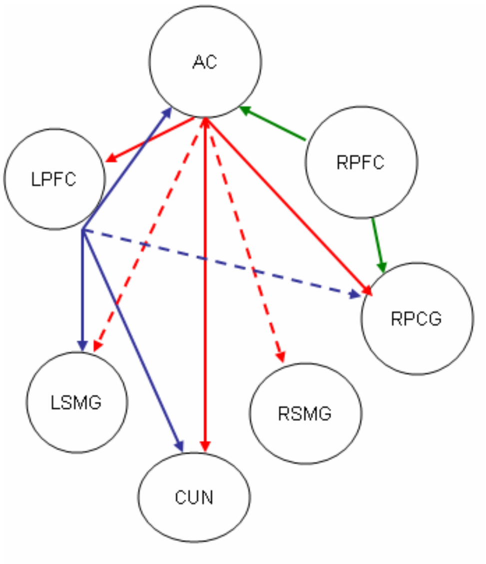

Figure 4 Schematic of partial correlations for the beta frequency (12 – 32 Hz) initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. The AC shows positive significant relationships with the LPFC, RPCG and cuneus, while having negative relationships with the LSMG and RSMG. The LPFC shares significant positive relationships with the AC, LSMG and cuneus and a negative relationship with the RPCG. The RPFC only shows relationships with the AC and RPCG for total beta power.

Table 9 Partial correlation analysis for the theta frequency (3.5 – 8.0 Hz) relative to training in 14 – 18 Hz for each ROT. In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.074	.362
LPFC	0.693	.000
LSMG	-0.152	.059
RPCG	0.019	.813
RPFC	0.102	.205
RSMG	0.038	.639
	LPFC	
Cun	0.038	.785
AC	0.618	.000
LSMG	0.184	.178
RPCG	-0.274	.043
RPFC	-0.065	.639
RSMG	0.281	.038
	RPFC	
Cun	-0.162	.237
AC	0.747	.000
LPFC	0.028	.842
LSMG	0.035	.798
RPCG	0.687	.000
RSMG	0.116	.398

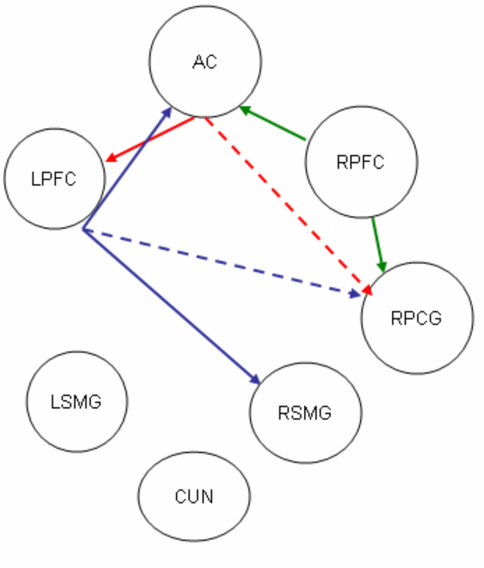

Figure 5 Schematic of partial correlations for the theta frequency (3.5 – 8.0 Hz) initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. The AC shares a significant positive relationship with only the LPFC and a negative relationship with only the RPCG. The LPFC shares significant positive relationships with the AC and RSMG and a negative relationship with the RPCG. The RPFC shares significant positive relationships with only the AC and RPCG in this frequency.

Table 10 Partial correlation analysis for the delta frequency (0.5 – 3.5 Hz) relative to training in 14 – 18 Hz for each ROT. In the table from right to left is the region of interest and correlation coefficient with region of training controlling for the remaining regions and the probability.

ROI	*AC*	*p*
Cun	0.152	.059
LPFC	0.331	.000
LSMG	0.135	.094
RPCG	0.080	.321
RPFC	0.027	.736
RSMG	-0.167	.038
	LPFC	
Cun	-0.241	.076
AC	0.675	.000
LSMG	0.230	.092
RPCG	-0.551	.000
RPFC	-0.081	.554
RSMG	0.453	.001
	RPFC	
Cun	-0.611	.000
AC	0.791	.000
LPFC	-0.253	.062
LSMG	0.536	.000
RPCG	0.738	.000
RSMG	0.128	.353

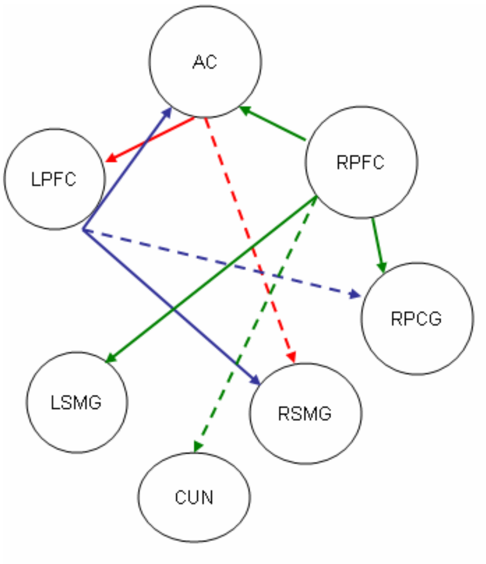

Figure 6 Schematic of partial correlations for the delta frequency (0.5 – 3.5 Hz) initiated by LNFB training in each of the ROTs controlling for respective ROIs. The red is for training in the AC. The blue is for training in the LPFC. The green is for training in the RPFC. The solid lines indicate significance at .001. The dashed lines indicate a significant negative relationship. The AC shares a positive relationship with the LPFC and a negative relationship with the RSMG. The LPFC shares positive relationships with the AC and RSMG and a negative relationship with the RPCG. The RPFC share positive relationships with the AC, RPCG and LSMG and a negative relationship with the cuneus.

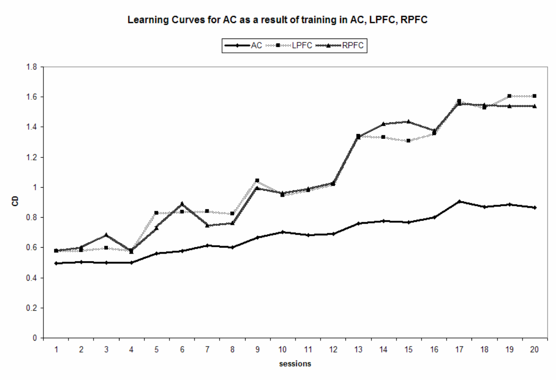

Figure 7 Learning curves for the AC as a result of LNFB training (14 – 18 Hz) in the AC, LPFC and RPFC. On the ordinate is the mean current density and on the abscissa are sessions. Training 14 – 18 Hz activity in the AC produces increases at lower levels training the AC than does by training each of the other ROT.

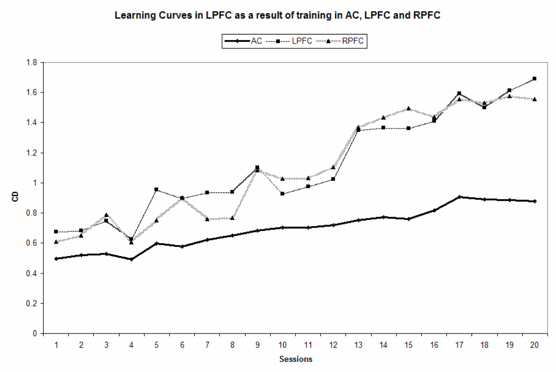

Figure 8 Learning curves for the LPFC as a result of LNFB training (14 – 18 Hz) in the AC, LPFC and RPFC. On the ordinate is the mean current density and on the abscissa are sessions. The LPFC increases in current density at lower levels as a result of training in the AC and increases at higher levels due to training in the LPFC and RPFC.

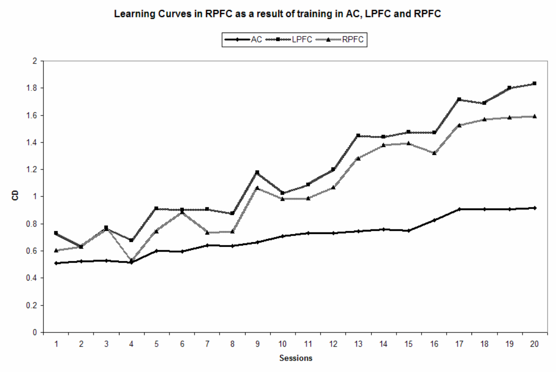

Figure 9 Learning curves for the RPFC as a result of LNFB training (14 – 18 Hz) in the AC, LPFC and RPFC. On the ordinate is the mean current density and on the abscissa are sessions.. Training in the AC shows an increase in the RPFC at lower levels than training in the RPFC or LPFC.

3:5 Subjective Reports:

Figures ten, eleven and twelve show the results of the subjective reports provided by the subjects at the end of each session. The reports are scaled according to the mental processes and strategies employed to obtain points during the training. The mental activities are WM = working memory – we consider this as using any type of mnemonic process to elicit activity in the specific region of interest; including, mathematics, use of foreign language, declarative memory and STM relating to memory of prior sessions in which they were successful; A = attentional processes - we consider this involving any attentive processing to internal and external stimuli; DAS = daily stressors – we consider this any report of thoughts to grades, tests, finances, or such outside stressors; V = visualization – we consider this visualization techniques, mental rotation, spatial organization or imagery techniques; Ap = Appetitive thoughts – we consider this any focus given to sexual imagery, food, hunger, and thirst; DS = dissatisfaction with performance – we consider this thought processes directed toward dissatisfaction with the game, with their points, and with the inhibitory factors; MV = mental verbalization – we consider this mental conversation with self, with the game, singing songs or swearing at the game. The AC subjects reported a tendency toward working memory and attentional processes, with an emphasis with working memory. The LPFC subjects report a tendency similar to the AC except the tendency is toward attentional processes. The RPFC subjects report a tendency toward working memory processes, with an apparent increase in MV and V as opposed to the AC and LPFC.

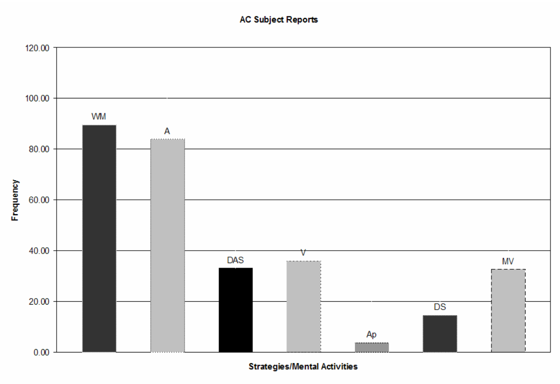

Figure 10 Subjective reports of strategies and mental processes used during the LNFB training in the AC. The activities utilizing working memory and attentive processes are the most frequent. Legend: WM = working memory; A = attention to self, relaxation, game or score on screen; DAS = daily stressors; V = visualization techniques; Ap = appetitive thoughts, i.e., hunger or sexual imagery; DS = dissatisfaction with performance; MV = mental verbalization, talking to the game, self, or singing songs.

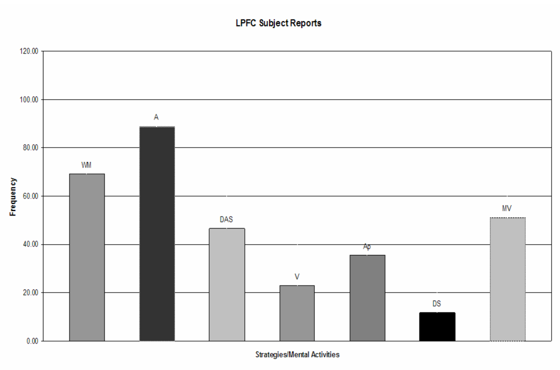

Figure 11 Subjective reports of strategies and mental processes used during the LNFB training in the LPFC. The activities utilizing working memory and attentive processes are the most frequent, with an emphasis on attention. Legend: as in Fig. 5.

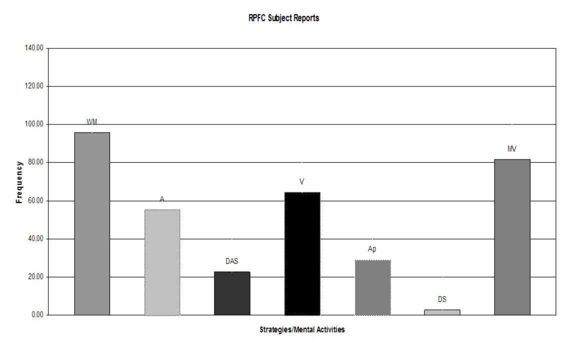

Figure 12 Subjective reports of strategies and mental processes used during the LNFB training in the RPFC. The activities utilizing working memory and mental verbalization processes are the most frequent, with visualization also increased as opposed to the AC or LPFC. Legend: as in Fig. 5.

3:6 Psychometric Results

The results for the comparison between pre and post psychometric scores (stage IV) indicate that LNFB training produced a mean increase of 10 points as for all regions of training, with the AC being the highest at 11. This is not entirely unexpected due to the group having a higher pre measure.

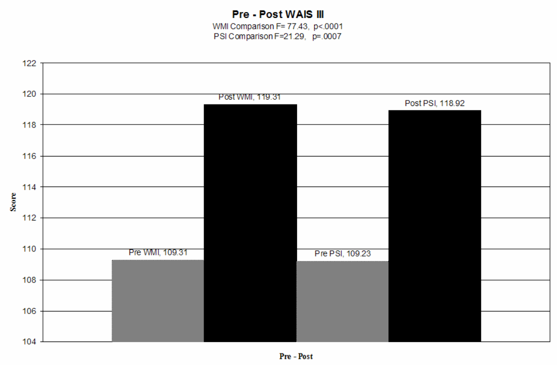

Figure 13 Mean WMI and PSI scores before and after the LNFB training for all groups combined.

Figure 14 Post training scores per ROT group. In the graph are the PSI subtest scores; SS = symbol search, CD = coding and the WMI subtest scores; AR = arithmetic, DS = digit span, LN = letter number sequencing.

4: Discussion:

This is the first study of its kind to evaluate the effects of traditional or spatial-specific neurofeedback training in the cerebral volume. The data offer further support to the efficacy of spatial-specific (LNFB) training in three distinct regions of the cortex that are shown to be functionally correlated (see introduction). Participants were able to increase activation patterns in each ROT over sessions at significant levels. We trained non-clinical subjects to increase 14 – 18 Hz activity in a cluster of neurons within a limbic region (AC) and two clusters of neurons within regions in the dorsolateral prefrontal cortex (LPFC and RPFC) and attempted to reasonably and soundly describe the nature of the relationship between each of these neuronal populations with other neuronal populations within cortical regions that are identified in the literature as being active in tasks involving attention, mnemonic, cognitive and executive processes (Bush, Luu, Posner, 2000; Nyberg et al, 2002, 2003).

In discussing executive attention we must take into consideration the limitations of the methods we utilized. When we refer to the respective ROIs; AC, RPFC, LPFC, LSMG, RSMG, RPCG and Cuneus – we are referring to regions delimited by a number of discrete brain volume elements (voxels) as defined by the standard head model we employed. Thus, the ROT (table 4) may be displaced as much as 3-4 cm. from the aimed ROI. Within these limitations, the data illustrates the efficacy of LNFB training. However, it appears that this methodology does not offer the possibility to train individuals to increase or decrease specific frequencies in specific regions of the cortex. Rather, it appears that networks of regions connected to the ROT are entrained at several frequencies. The data seems to illustrate the functional relationship between these three ROTs and clusters of neurons within six other ROIs according to frequency. The data suggests that neurofeedback in any given frequency is not restricted to effects for that particular frequency; rather there is cooperation among frequencies relative to task and ROI, in essence a layering-effect for task and frequency. If this is true, then LNFB may be a tool to study or possibly influence and strengthen networks of related functional units in the brain. This speculation should be further studied. In the following subsections we will address the results according to region of training in an attempt to interpret the present results.

LNFB training 14 – 18 Hz produces effects in delta frequency for each ROT, which is possibly related to the encoding of information relative to task; higher cognitive functioning is reported to involve slow synchronization of the delta or theta frequency over longer distances (Lubar, 1997), while faster frequency bands are reported to involve local neuronal populations (von Stein, et al, 1999). The RPFC, AC and RPCG show a consistent pattern of positive interactions as a result of training the cluster of neurons within the RPFC.

The theta frequency shows differential effects as a result of training in each ROT, and expounds a lesser degree of involvement for all regions; however, this may be a more specific to functional encoding of information from regions involved in spatial orientation, this is possibly attributed to the posterior regions being involved in the evaluation of visual and sensory information and encoding into memory, since the encoding of episodic (short term) and working memory processes seem to be reflected by oscillations within the theta frequency band (~4-8 Hz) (Klimesch, Doppelmayr et al. 1997; Klimesch, Doppelmayr et al. 1999) within a thalamo-hippocampal-cortical system (Klimesch 1996; Burgess and Gruzelier 1997; Fell, Klaver et al. 2003). During encoding the increase in theta is significantly larger for items that can later be remembered (Klimesch 1996; Klimesch, Doppelmayr et al. 2001). Theta amplitude also increases with increasing memory load during a memory retention interval, reflecting a specific role for theta in maintenance of the memory trace. Moreover, theta synchronization is maximal during retrieval, and the amplitude of Theta synchronization during retrieval predicts retrieval success (Klimesch 1999; Fingelkurts, Krause et al. 2002; Jensen and Tesche 2002).

The alpha 1 frequency shows substantial differential effects as a result of LNFB training in each ROT. The training in the AC appears to increase communication between anterior and posterior regions of cingulate cortex, and encoding processes with LPFC. The LPFC, on the other hand may be more involved in the strengthening of encoding and mnemonic processes relative language, attention to physical state and other sensory information. The RPFC on the other hand continues to show this consistent pattern involving RPFC, AC, LSMG yet no relationship with cuneus or LPFC. This is not the first occurrence of this, and offers evidence against the idea that the left and right PFC work in conjunction in memory processing. It may infer that the RPFC (at least this cluster of neurons) is directly associated to attentional monitoring along with the AC and RPCG, and possibly an effect for visual and spatial encoding of attentional and memory processes relating to the game and evaluation of thought processes needed to achieve the desired result. The alpha 2 frequency shows effects for positive associations in similar regions as alpha 1; however, the negative relationships for the dorsolateral ROT appear to become specific to posterior cingulate in this frequency. This result is the possible attention to working memory processes, that is to say the processing of external and internal stimuli requires an equal portion of attention from the right hemisphere. The alpha rhythm (~8-12 Hz) is generated mainly by corticocortical and thalamocortical neural networks (Steriade, Gloor et al. 1990; Klimesch, Schimke et al. 1994; Klimesch, Doppelmayr et al. 1997) and research suggests distinct roles for lower (~8-10 Hz) and upper (~10-12 Hz) alpha band activity in cognition. The lower band relates primarily to response readiness and attentional demands (Klimesch et al., 1992), and plays only an indirect role in memory. By contrast, oscillations in the upper alpha band have been consistently observed during (semantic) long-term memory processes (Klimesch, Schimke et al. 1994; Klimesch, Doppelmayr et al. 1996; Klimesch, Doppelmayr et al. 1998). In contrast to the theta band, higher alpha amplitude at rest, and lower alpha amplitude during task performance, (reflecting a large alpha suppression during task), is correlated with efficient memory performance in healthy adult subjects (Klimesch, Doppelmayr et al. 1997; Vogt, Klimesch et al. 1998; Klimesch 1999; Stipacek, Grabner et al. 2003).

The beta frequency shows effects for all ROT as a reslt of LNFB training. The AC appears to be involved with more regions in this freuqncy. This effect is plausibly related to a learning effect, response conflict and resolution, motivation and goal direction, viz. that the AC directs the other regions in both lower and higher frequencies necessary for completion of task and directs the RPFC to follow suit and coordinate the load for attention.

The partial correlations offer intricate details regarding the relationship between these ROIs and the effects if LNFB training in each ROT. The psychometric scores indicate that LNFB training influenced an increase of 10 points. The AC group averaged 11, which is not unexpected since this group scored higher at pre-testing. Figure 13 shows the individual post subtest scores for each ROT group. This graph shows the AC influenced higher subtest scores, except in the SS and CD subtests, while the LPFC and

RPFC show higher influence on SS. These scores and their correlations with the regions of interest are the topic of a more intense analysis for a future work. The subjective reports provided by the participants in this study provide a number of insights into the differences between hemispheric processing of the DLPFC and AC. Executive attention, memory, cognition and the roles of the AC and DLPFC and associated frequency patterns are areas of interest for our lab and future works will attempt to define and describe the specificity with which regions and frequencies interact to regulate executive attention.

Conclusion:

Given the dynamic processes of the brain and the intricacies of cortical networks, LNFB may be a plausible methodology for the training or strengthening of cortical networks, which in effect, may be the very source of the neurofeedback process. This will be a direction for further study. There are several noteworthy patterns revealed in this data in all frequencies; (1) it appears as if the AC and LPFC do not communicate with the RPCG at the same time in any given frequency; (2) the AC appears to share no direct afferent relationship with the RPFC, it is apparent that it receives information rather than projects information – it is possible that attentional processes are regulated by thalamic nuclei with afferents to this region in RPFC; (3) regardless of frequency, training in RPFC shows effects for AC and RPCG, it is possible this is the right hemispheric attentional network literature refers to and it is monitored by another specific region (4) AC and LPFC are significantly correlated in all frequencies, suggesting afferent and efferent connectivity patterns; (5) the AC and cuneus communicate only in alpha or beta frequencies, long term communication in slower frequencies is not demonstrated. The results require further study and replication. Our future research directions involve larger sample sizes and selecting regions of training to further our understanding of the dynamics of cortico-cortical networks and the fundamental regions and frequencies involved in executive functions; including cognition, memory and executive attention.

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