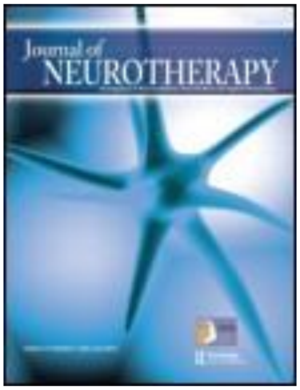

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Intentional Increase of Cerebral Blood Oxygenation Using Hemoencephalography (HEG): An Efficient Brain Exercise Therapy

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This paper is dedicated to the fond memory of Antoine Rémond who provided many of the original ideas towards the development and application of this instrumentation. He was particularly interested in the psychological impact of the technique. His insights and support are sorely missed.

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SUMMARY. Intentional enhancement of regional cerebral blood oxygenation ($rCBO_2$) in specific cerebral locations was studied as a brain exercise. A review of literature showed the effect of brain exercise on brain physiology. Hemoencephalography (HEG), a graphic analog of brain blood flow of oxygenated hemoglobin indicated by non-invasive infrared spectroscopy, was used to guide intentionally increasing $rCBO_2$. A musical note and visual graphic keyed to changes in cortical blood oxygenation was provided to the participant. A primary aim of this study was to demonstrate the capacity of subjects with brain disorders to increase oxygenation of selected brain tissue using HEG and test the hypothesis that multiple repetitions of these brain exercises improved sustained attention measured with a continuous performance test. The impulsivity score for subjects in the exercise group was in the normal range after 10 sessions. In a small set of subjects, low arousal SPECT images showed increased vascularity after 30 half-hour sessions of intentional enhancement of local blood oxygenation.

KEYWORDS. Brain blood flow, hemoencephalography, HEG, brain exercise, ADD/ADHD, toxic encephalopathy

INTRODUCTION

Research has demonstrated that interventions activating the brain can result in brain growth. Diamond et al. (1975) demonstrated the positive effect of an activating sensory enriched environment in promoting the growth of dendritic density and vascularity in mouse brains. In autopsy studies, the effects of human functional brain exercise found an association between the complexity of the dendritic systems of the hand-finger primary sensory receptive brain area and the nature of work of the individual (Scheibel, Conrad, Perdue, Tomiyasu, & Weshler, 1990). Similarly, Jacobs, Schall, and Scheibel (1993) found that education had a consistent positive effect on dendritic density. Albert, Painted, Weinbruch, Rockstroh, and Taub (1995) found the cortical representation for the fingers of the left hand in string players increased in size and correlated inversely to the age at the start of musical practice. Maguire et al. (2000) found London cabbies, renowned for their encyclopedic knowledge of London streets, have enlarged right posterior hippocampi. Weiskopf et al.

(2003) showed voluntary activation of the anterior cingulate gyrus with fMRI feedback.

Physiological changes in brain activation (i.e., brain exercise) can be measured by a voluntary technique of Hemoencephalography (HEG; Toomim & Marsh, 1999; Toomim, 2002). This was validated with voluntary control of brain blood flow shown by Yoo and Jolez (2002) with students showing voluntary enhancement of selected brain areas with the aid of fMRI biofeedback. This activation is contrary to the present day practice of "bottom up" functional activity such as physical therapy applied to a limb, in which limb movement is used therapeutically to intentionally activate an impaired anatomic brain location. While the activation of a brain function referent to a desired anatomic area is possible, it is often inefficient for a variety of reasons. In contrast, rehabilitation of brain functions, by sustained direct brain activation may show enhanced recovery of normal function (Robertson & Murre, 1999). This "top down" training in function-based exercises is intended to activate hypoperfused brain volumes, but may also activate unrelated brain volumes with a consequent efficiency penalty. Further, the brain tends to direct function away from damaged areas and activates alternative algorithms and areas for problem solving. For example, Taub et al. (1993) found that monkies with brain infarcts did not utilize rehabilitated neural pathways generated by newly learned limb control, but instead they reverted to use of the unaffected limb wherever possible.

Since we cannot assume that a damaged brain uses a functional algorithm in the same way as a healthy one, bottom up functional activation of higher brain functions could be a poor candidate for a reactivation strategy. Hoshi et al. (1994) found that mental arithmetic did not activate the frontal region of the dominant hemisphere in some subjects. They suggested that particular mental functions are not found at the same position for everyone in that some left-handed people have reversed brains (their left and right hemispheres are interchanged) and development of a means for locating the required training site is required.

Tokarev and Fleischman (1988) used cerebral rheoencephalography biofeedback on workers in a soviet factory and found improved worker error rates resulted from several applications of his technique. This suggested that active intervention aimed at increasing cerebral blood flow in humans is possible and results in improved brain function. Boynton, Engel, Glover, and Heeger (1996) developed data supporting a proposed linear relationship (accounting for 86.81% of the variance) for fMRI response and neural activity averaged over a small neural volume in a short time interval. In the present study, we extended this model by proposing that long lasting physiological changes, improvement in brain function, were linearly related to average intentional brain blood oxygenation increases.

These historical developments suggested that research on the effects of intentional increases of cerebral blood oxygenation (CBO_2) via HEG feedback from specific sites upon performance of instructions to increase HEG indications was needed. A simple spectrophotometer allowing the assessment of cerebral blood flow via light shown through the intact scalp (Jobsis, 1977) made possible the efficient activation of selected localized brain tissue using a process now known as Hemoencephalography (HEG). This instrumentation, used for assessment of $rCBO_2$ by light shown through the skull, has undergone extensive development by Britton Chance at the University of Pennsylvania (see Elwell & Hebden, 1999). This technology showed that signals can be used to enable voluntary modulation of cortical blood flow and consequently, the changes in blood flow can improve brain function. Preliminary data from pilot experiments showed that the location of the feedback system, not expectation or intent of the subject to maintain the feedback at a perceived area, determined the location of the effect of the sound-guided effort. Cognitive function studies using the differences between blood flow images before and after activation showed that exercise of a specific brain function activates a number of small but scattered tissue volumes related to the performed function (Posner & Raichle, 1998). While normal brain functioning redirects local blood flow to the functional area, the HEG technique allows a therapist and client to choose an area for activation. HEG allows the maximization of blood oxygenation by training a chosen head position, the brain then increases blood flow guided by the intent to maximize the feedback. This approach, combined with educational drills as brain exercises, can maximize blood oxygenation directly in selected brain areas.

Brain imaging studies have used defined cognitive activities to locate correlated changes in regional cerebral blood flow (rCBF) and/or regional metabolic products (Posner & Raichle, 1998). In fMRI imaging studies of blood flow, subjects are given instructions to "do" something and the implication of "intentionality" was not examined. In the present study, localized $rCBO_2$ measures at prefrontal brain regions were voluntarily increased as much as possible to measure the effect on impulsivity, a component of a continuous performance test. The hypotheses of this study were: (a) intentional increases in HEG signals at a given anatomic site can be demonstrated consistently, and (b) maximizing HEG at pre-selected brain regions in brain-impaired patients improves post-training scores compared to pre-test values on a measure of sustained attention.

METHODS

Participants

All participating individuals or the parents of minors signed informed consent forms. The exercise group (n = 8) consisted of patients with clinical problems unselected for age or gender. They were referred by their physicians. Diagnoses included Attention Deficit Disorder (12), toxic encephalopathy (4), stroke (1), depression (4), chronic fatigue (1), traumatic brain injury (2), aging memory loss (1), autism (1), schizophrenia (1), and bipolar depression (1). For the 18 adults (10 male, 8 female), the average age was 40 (SD = 9.4). For the 10 children (9 male, 1 female), the average age was 10.65 (SD = 2.27) years. All children in the exercise group were diagnosed ADD or ADHD. None of the children were medicated at the time of testing or treatment. The study did not interfere with or alter any subject's treatments under their doctor's care. No medication changes were recommended or reported during the treatment or testing phases. A comparison group (n = 25) was formed of participants who answered an advertisement posted on college bulletin boards offering participation in an experiment directed toward brain improvement.

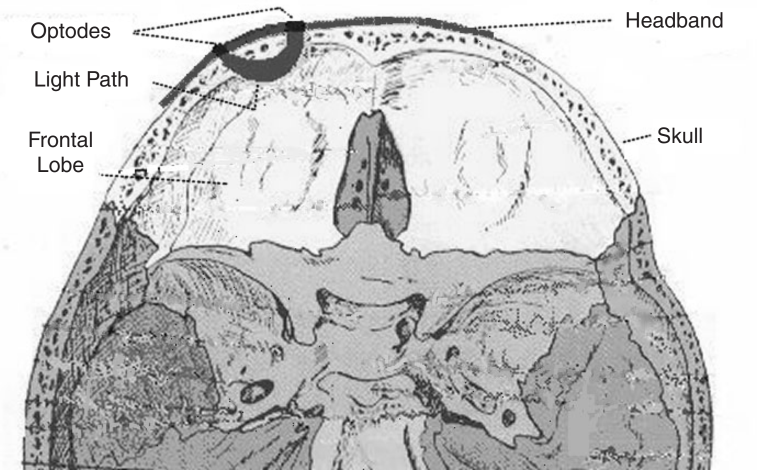
Equipment

HEG technology utilizes the translucent character of biological tissue. Biological tissue conducts diffused radiant energy of many kinds over a broad range of wavelengths. Closely spaced red and infrared light emitting diodes (LED optodes), the light source, and an optode light receiver were mounted on a headband separated from each other by three centimeters. Both the electronics and the headband were carefully designed and constructed to prevent inter-optode light leakage and/or external ambient light from affecting measurements. Figure 1 shows the location of the LED optodes on the skull. Effective depth of penetration in the highly vascular cortical tissue is about 1.5 cm directly below the mid-point between the optodes. The entrance and exit light areas were 0.052 cm^2 at the skin surface. The light entrance and exit points and the refractive and scattering qualities of the tissue form a banana-shaped light field. The form of the optical path is discussed by Chance (1992), and Benaron, Kurth, Steven, Delivoria-Papadopoulos, and Chance (1995).

The lights are alternately emitted onto the same skin surface. The emitted light penetrates these tissues and is scattered, refracted, and reflected. A small consistent amount of light modified by absorption of wavelength sensitive tissue returns to the surface and is measured (Jobsis, 1977; Chance, 1992). The red wavelength (660 nm) light source is less absorbed by oxygenated hemoglobin than by deoxygenated hemoglobin and with tissue utilization. The reference, infrared light source (850 nm), is relatively unaffected by the degree of hemoglobin oxygenation changes. Capillary oxygenation is only slightly affected by peripheral blood pressure and is controlled principally by energy demands of the tissue. Oxygenated hemoglobin concentration is therefore a convenient, useful measure of local blood flow.

The ratio of the received red to infrared light has a useful property. The numerator and denominator of the ratio are subject to the same attenuation due to skin, skull and path length. In this ratio these variables cancel. The HEG ratio is the basis of blood flow training. A normalized basis for HEG was established using measurements at Fp1 of 154 adult attendees at professional society meetings. A normalized reference value of 100 (SD = 20) was thus established and served to calibrate all further spectrophotometers.

FIGURE 1. A top-down view for the location of the LED optodes.



The graphic representation of HEG values presented to the subjects consisted of a dynamic histogram of successive colored vertical bars keyed to the HEG ratio. Changes in the brain oxygenation were thus indicated by changes of both the current bar length and a musical note. The current bar, reflecting shifts in local cerebral blood oxygenation, varied rapidly in length and was updated 16 times per second. At eight and one-third-second intervals the current bar was replaced by a "fixed" bar equal in length to the average of the current bar in the preceding interval. A new "current" variable bar was then displayed in the next rightmost space on the display screen.

The radiation power of the incident lights was designed to be far below the level of normal light intensity on the scalp. Power for both wavelengths at the cortex is greatly attenuated from skin surface level by absorption and scattering in penetrating the skull before impinging on the brain. Red luminous intensity for the Stanley BR1102 LED (660 nm) at 13 milliamperes average at the skin surface is about 1% of sunlight exposure for sun at the horizon. Skin surface infrared luminous intensity for the Stanley AN1102W LED at 5 milliamperes average is 0.01% of sunlight at the emitted wavelength (850 nm).

Procedure

The subjects were self-scheduled between 1 and 6 p.m. at their convenience for the 10 sessions. For the exercise group, the HEG equipment was applied to the forehead of the subject who was provided audible and visual feedback of the HEG signal strength. The subject was instructed to use the system to increase the signal. The HEG readings were displayed on a computer monitor as a sequential bar histogram. The subject was free to use either auditory or visual feedback, or both, as a guide to the immediate effectiveness of efforts to increase $rCBO_{2.}$ The values of the initial eight and one-third second averaged bar and subsequent 71 equally timed average bars (10-minute segment) were compiled for all placements for all subjects (3 segments, 30 minutes total).

The exercise group was instructed to maximize the HEG indications of increases in $rCBO_2$ in each of three 10-minute segments comprising each session of the 10-session program. The sensitive area of the headband was placed on a line four cm above the pupils of the eyes in the following order for successive 10-minute segments: Fp1, Fpz, and Fp2. The training covered a horizontal band across the forehead. For the purposes of linearity calculations in this study, only the measurements at Fp1 were considered. A two- to four-minute rest period separated segments. The sensitive area of a red/infrared spectrophotometer was non-invasively and successively trained on the skin surface at designated positions per the 10/20 EEG montage standard. The exercise group targeted increases successively in session segments at Fp1, Fpz, and Fp2.

Enhancement of $rCBO_2$ for all three segments of a session was required for the exercise group but only for the first segment of each session for the comparison group. This approach allowed us to focus the treatments on small, well-defined areas with experimental consistency for Fp1 between groups. The process of required concentration was demonstrated to each subject by the problem of reading extremely small type. Each reading success was countered with moving the visible target farther away until success was no longer possible. Then attention was directed to the feeling engendered by the effort. When this feeling was demonstrated consistently, it was then applied to the quest for increased HEG readings (i.e., intensity of intent).

The comparison group received similar instructions for maximization and was allowed to develop individual strategies for the remaining two segments of each session. The comparison group targeted increases in Fp1 for the first segment, then Fpz was decreased in the second segment, and Fp2 was held constant at an intermediate value in the third segment. This strategy was expected to allow outcome comparisons between the two groups for "positive" treatment time and intent approximately in the ratio of one to three.

Subjects in both groups were carefully instructed to avoid the performance of specific cognitive tasks. A task-specific brain area unrelated to the targeted exercise area, if activated, would detract from the intent of the treatment exercise. Participants were told to maintain concentrated attention, as above described, to the sound and/or graphics as guides for change. They were given positive comments on successful trials. These instructions were designed to maximize the HEG value.

For each subject, the HEG data were compiled and examined for the initial eight and one-third second value and the 10-minute segment average value at Fp1 for each of the 10 sessions. A gain index, defined as: Gain = (segment average)/(initial average) − 1, was computed for each subject for each Fp1 segment. An individual subject master index averaged over the 10 sessions was then computed. The subject master index represented the gain made by each subject at Fp1 over the ten sessions.

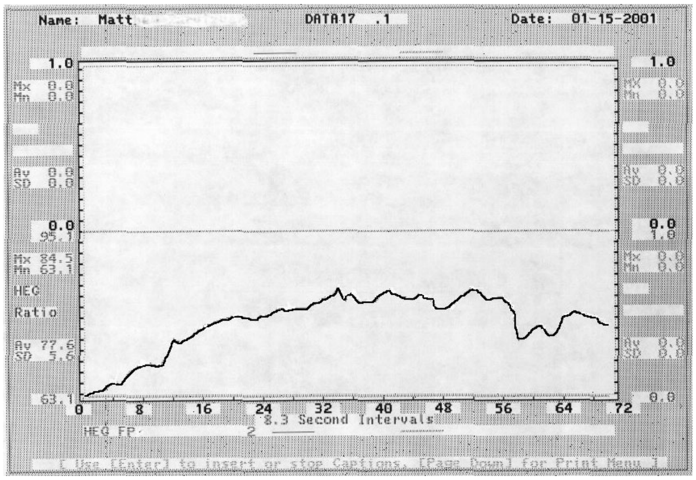
The Test of Variables of Attention (TOVA) completed before and after the 10 HEG sessions was the dependent variable in this study. The standard scores for attention, impulsivity, reaction time, and reaction time variability were measured by TOVA. Non-linearity in TOVA scoring is noted. Scores less than or equal to 40 are given a floor value score of 40 by the TOVA designers. Because this non-linearity is undesirable for statistical analysis, we eliminated four subjects with TOVA scores of 40 from HEG TOVA comparisons.

RESULTS

No subject reported any negative experiences resulting from HEG apart from an occasional transient mild headache and fatigue. The HEG vs. Time shown in Figure 2 illustrates changes in cerebral blood oxygenation ($rCBO_2$) resulting from intentional HEG activity.

The graph in Figure 2 shows the progress of a two-minute effort to increase $rCBO_2$ at Fpz. When queried for the method and approach used, the subject stated, "The increments occurred in response to an intense desire to increase the graphic indications with no additional thought." Circulatory increases produce no brain sensations and the changes were perceived only as feedback from the graph and sound. The subject was continuously informed of progress toward increasing $rCBO_2$ at the chosen location, and accomplished that end efficiently. Impulsivity TOVA gains were computed for all subjects. The adult and child groups were also separately com-

FIGURE 2. The change in $rCBO_2$ at Fpz over two-minutes.



puted for all subjects. They were ranked according to *initial* TOVA values and divided into upper- and lower-ranked groups. The adult and child groups combined and separated are reported in Table 1.

Comparison of the gains made with training for both children and adults was better for the lower-scoring halves of both groups. For the TOVA value, lower initial TOVA values presage larger TOVA improvements (see Figure 3).

The histogram shows the detailed distribution of the exercise group's TOVA gains and losses for each of the four TOVA score domains: omission, impulsivity, reaction time, and reaction time variability. The horizontal axis divides the subject gain scores into value intervals of 10 scores each. The vertical axis sums the number of cases in each of the exercise group's TOVA score domains that fall within each 10-score group. At a glance one can see the distribution of scores for each domain across the population. It is clear that the lower positive 10-score group dominates the TOVA distribution. The sum of all positive scores is clearly much larger than the sum of negative scores.

In HEG or EEG neurotherapy the question of the effect of the number of days between sessions often arises. Table 2 shows the observed effects of time between sessions on the efficiency of training sessions in the experimental group. It is noteworthy that efficiency is negatively impacted by increased session frequency and therefore, more sessions are needed to gain equal results. These observations roughly agree with the report of Stickgold, LaTanya, and Hobson (2000) on the effects of slow wave sleep on intrinsic learning.

A regression analysis on a least squares line through the origin of the individual TOVA impulsivity gain indices [(final/initial)−1], versus

TABLE 1. The gain in TOVA scores for adults and children.

		TOVA IMPULSIVITY		HEG Index FP1
	Initial TOVA_{imp}	**Final** TOVA_{imp}	**Percent Gain/Session**	**Percent Gain/ Session**
All Subjects	**87.4 ± 0.70**	**98.5 ± 0.47**	**12.70**	**14.0**
Adult Means	**83.2 ± 1.10**	**95.4 ± 1.20**	**15.8**	**13.0**
Upper half	103.0 ± 0.97	105.8 ± 0.82	3.02	13.4
Lower half	63.7 ± 1.3	85.2 ± 1.5	33.7	12.6
Child Means	**94.9 ± 1.3**	**102.0 ± 0.97**	**7.5**	**15.7**
Upper half	103.0 ± 0.8	104.0 ± 1.82	1.5	18.3
Lower half	87.1 ± 1.9	99.8 ± 0.91	14.5	13.0

FIGURE 3. TOVA gain scores for upper- and lower-ranked groups.

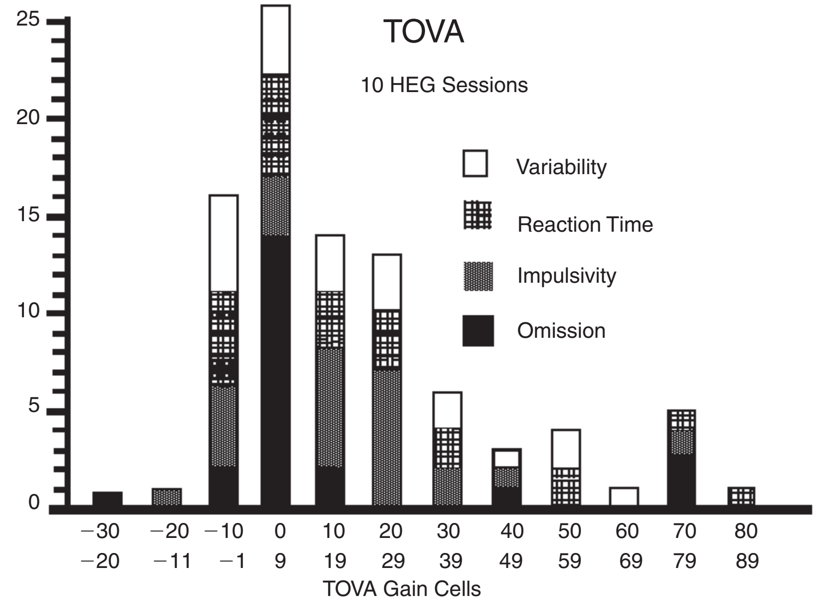


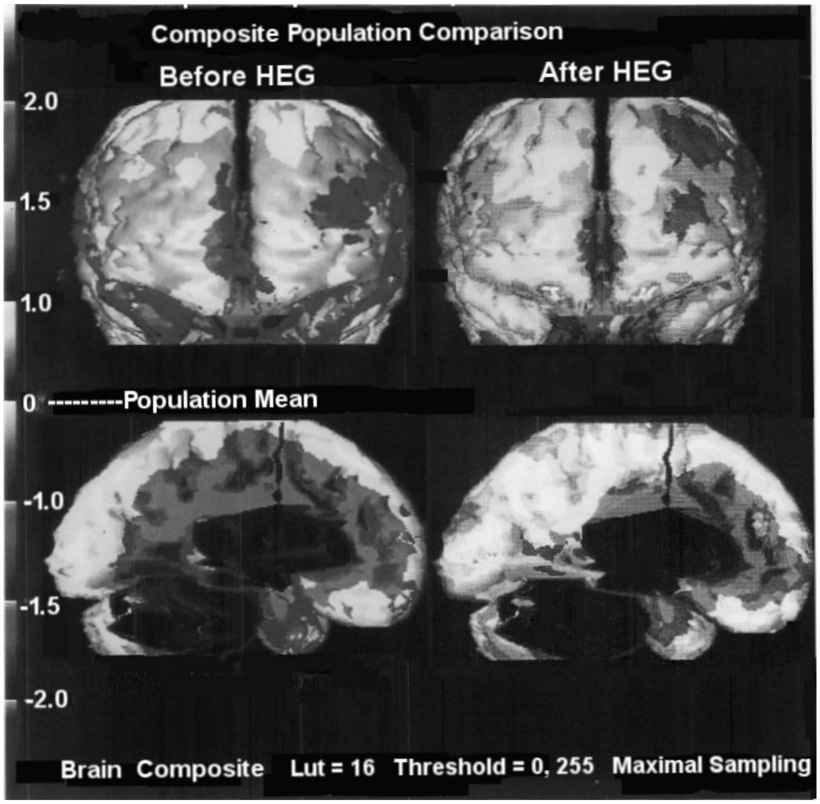
TABLE 2. Effects of days between sessions on TOVA gains resulting from HEG training.

Days between sessions	3.0 to 3.5	3.6 to 4.0	4.1 to 5.0	5.1 to 7.0
TOVA increase	9.75	16.82	17.39	15.75

individual HEG gain indices for the participants of the exercise group, was calculated and a significant relationship was found ($r = 0.746$, $r^2 = .55$ $df = 1$, $F = 26$, $p < .001$). The least squares fit of a straight line through the origin of the TOVA impulsivity data thus accounts for 55% of the variance. T-tests of the 28 experimental group subjects TOVA gains versus their paired HEG gains yielded ($t > 5.0$, $df = 27$, $p < .001$).

Figure 4 shows the SPECT blood flow images before and after training in the case of a 67-year-old female diagnosed with memory loss, anxiety, depression, and high blood pressure. This example was chosen to illustrate the effect of HEG training on blood flow patterns. In this case, HEG training time was applied variously to T3, F7, Fp1, Fpz, Fp2, F8, and T4 (a band line around the forehead) to address the hypo-

FIGURE 4. SPECT blood flow images before and after training in a 67-year-old female.



perfused area shown on the initial SPECT. Vascular improvement is shown in the frontal and temporal lobes at the specific training sites. The cingulate gyrus effect illustrates indirect benefit for related tissues. The SPECT images after HEG show increases in blood flow in areas corresponding to the training sites.

DISCUSSION

Children and adults who scored in the lower half of the TOVA initial score list made far greater gains than those in the upper half of TOVA scores. The adults had greater TOVA gains than the children (12.3 vs. 7.1). Adults started from a lower initial TOVA score than children (83.2

vs. 94.9). HEG gains for children were 20% greater than for the adults. In spite of this advantage their TOVA increases were about half, 57%, that of the adults. This suggests that low initial TOVA scores may estimate training success. The improvement in TOVA scores of 1.1 points per session (PPS) with an initial TOVA value of 85.9 exceeds to other EEG ADD brain therapy studies using the TOVA. In these studies, Monastra, Monastra, and George (2002) reported TOVA PPS of 0.54; Kaiser and Othmer (1997) reported PPS of 0.49; Rossiter and La Vaque (1995) reported PPS of 0.55 and Thompson and Thompson (1998) reported PPS of 0.48. These studies reported initial TOVA values in the range from 72 to 85. Increased blood flow in the skin could account for some part of HEG increases. However, the question of whether the measured oxygenation increased during HEG is in brain tissue and not in surface skin has been discussed in a review of optical technology by Villringer and Chance (1997), Kurth, Steven, Benaron, and Chance (1993) and Germon, Kane, Manara, and Nelson (1994). The results show that only 5 to 10 percent of the HEG output comes from skin and skull tissues. The possibility that blood flow in scalp tissue might significantly affect the HEG reading was studied with a thermistor temperature probe responsive to 0.01 degree Fahrenheit placed on the forehead centered between the spectrophotometer light source and receiver. There was no measurable temperature increase and therefore no measurable skin blood flow increase, while the HEG value increased eleven percent.

The results of this study may be a small step along the way toward harnessing the brain's plasticity for development and repair. As a dynamic system, the brain may be continually degenerating and regenerating to maintain equilibrium at its current volume. Intentional brain activity can then raise the current level to a more useful condition and the "Use it or lose it" (Diamond et al., 1975) metaphor may be applicable. HEG provides a simple way to increase neural demand for energy to fuel the basic angiogenic and neurogenic processes that support brain plasticity. "Neural progenitor cells proliferate in response to growth factors that are associated with angiogenesis . . ." (Palmer, Willhoite, & Gage, 2000) and it is certainly possible that the increased blood flow after HEG training may be the result of angiogenesis.

Early data with HEG strongly suggested a linear relationship between TOVA and the effort required to increase HEG. It was expected that the group using one-third as much time increasing HEG would gain one-third as much in TOVA as an experimental group. The comparison group was formed to test this hypothesis and gained 4.2 TOVA impulsivity points while the exercise group gained 12.25 points. The gains ratio of 12.25/4.2 = 2.94 is extremely close to the expected 3 to 1 relationship. The standard deviation of the comparison group's gain was 33% of its average. Unfortunately, the highly variable values of the comparison group data relegate this result to nonsignificance. This variability most likely originated in instrument failures undetected by the less experienced comparison group operator, differing treatment instructions, or failures in the early headband design. During the process of data collection there were several malfunctions of the headband. Some breakdowns, invisible to the untrained eye, caused data to be collected with a faulty instrument. A common fault was intermittent connection to the optodes and/or intruding hair causing skin contact optode failure. Naturally then, incorrect averages or initial values were sometimes collected. Drift in calibration was not quantified. The significant variable could be the life expectancy of the LED light sources. It is highly likely that the positive effects in the treatment groups were reinforced by the synergy between the three training sites: FP1, FP2 and FP3.

The high correlation coefficient and SPECT findings are suggestive of a strong relationship between TOVA gain and HEG gain and support the second hypothesis of this study (maximizing HEG at pre-selected brain regions in brain-impaired patients improves post-training scores compared to pre-test values on a measure of sustained attention). Further, the improvement in post-treatment SPECT scans supports the relationship of HEG training to physiological changes. Pre- and post-treatment SPECT images under low arousal conditions demonstrated that effortful HEG training exercise of the brain led to improved perfusion patterns. Typically these showed increased cortical flow in the treated frontal and temporal lobes as well as the untreated posterior cingulate gyrus.

There is a question whether the treatment effect is due to regression to mean values. There were a variety of disorders treated in this study. Both group's initial TOVA scores were below the normal range. Each participant had ample time before treatment to regress to a mean. All were more than two years since diagnosis. Further, severe brain disabilities such as the disorders of many subjects in this study, have been shown to be long lasting. These results strongly suggest a new dimension of brain therapy results from an easily learned ability to direct blood to deficient areas of the brain. The inexpensive, portable instrument system comprising HEG, its simple application, and ease of learning cortical blood oxygenation and flow may make it practical to use in many therapy situations. HEG effects provide therapists, physicians and scientists the means to explore and develop an extensive new field in both therapeutic and basic behavior research (Weiskopf et al., 2003).

Ten sessions may not optimize the effect of this treatment technique. Future studies are needed to examine HEG with particular brain disorders when training is continued until plateau effects are noted as in the upper half of the TOVA initial value-ordered list. The newness of this technology and the small size and limited time of this study did not allow definition of floor or ceiling effects.

Studies limited to homogeneous groups of brain dysfunctional areas are needed to enhance our knowledge of specific treatment methodologies. In this study, the treatment effort was distributed over three sites in the exercise group. While this broadens its potential impact, it confounds the issue of quantity of therapy versus variety of sites of application. Studies with treatment and control groups matched for dysfunction, brain location, severity, and type are needed for clarity in the choice of therapy for these disorders. Assessment of suitable training areas needs further explanation. Future studies of brain activation need clinical attention to behavioral outcomes. Before and after behavioral testing focused not only on cognitive-specific brain functions but also on social characteristics is desirable. Efficacy over a broad range of conditions is suggested by the positive results of this study. Efficacy for any given condition needs support by directed activation of the affected brain areas. Connectivity of brain areas is, however, unavoidable. Treatment directed to major dysfunctional areas may also take advantage of this interdependency in specific disorders.

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