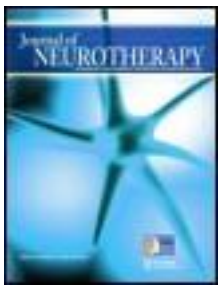

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QEEG Correlates of Auditory-Visual Entrainment Treatment Efficacy of Refractory Depression

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SCIENTIFIC ARTICLES

QEEG Correlates of Auditory-Visual Entrainment Treatment Efficacy of Refractory Depression

David S. Cantor, PhD
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ABSTRACT. *Introduction.* It is well established that the number of people diagnosed and suffering from depression is on the increase. Many of these patients are not responsive to first-line pharmacological intervention or simply cannot use medications for other reasons. As such, there has been a growing need for nonmedication approaches to treatment. The purpose of this study was to examine the use of auditory-visual EEG entrainment (AVE) at a 14 Hz (beta) frequency to decrease symptoms of depression with corresponding changes in neurophysiology.

Method. Sixteen participants ranged in age from 20 to 67 years and were screened utilizing the Beck Depression Inventory–II (BDI–II) and broken into two groups of 8 (simulated, AVE treatment groups), with a cross-over design. Both groups were given the BDI–II and QEEG testing at baseline, 4 weeks following either AVE or simulated treatment, and then again after an additional 4 weeks and a switch in treatment in the cross-over design.

Results. Results revealed significant reduction of depression only after the 4 weeks on AVE therapy of the BDI–II scores ($p > .01$). QEEG scores adjusted for normal age deviations demonstrate significant EEG change scores over time in cortical regions associated with mood regulation.

Conclusion. The findings indicate that AVE therapy may be a viable nonmedication therapeutic intervention.

KEYWORDS. AVE, audio-visual entrainment, depression, neurotherapy, QEEG

BACKGROUND

Depression is among one of the leading mental health diagnosis in America and affects approximately 18 million people of all ages (National Institute of Mental Health, 2001). It has been described as an epidemic and is ranked as one of the major health problems affecting Americans of all ages including children, adolescents, adults, and

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the elderly. Depression or affective disorders are neuropsychological and emotional in origin affecting moods, feelings, behavior, and physiology (National Institute of Mental Health, 2001). Current treatment trends include such treatments as medication, psychotherapy, alternative medicine approaches, and auditory-visual entrainment/stimulation (AVE). Antidepressant medications have become the first line of treatment for depression by most physicians. An estimated 50% of people suffering from depression are undiagnosed, misdiagnosed, undertreated, or not treated at all, yet according to some estimations as many as 90% of people with depression can be treated successfully (Broadhead et al., 1990).

With the increase in the amount of people taking antidepressants there has been an increase in people having difficulty tolerating medications or suffering severe side effects (Glenmullen, 2000). Antidepressant medications are expensive and there are no studies of the effects of their long-term use. Studies have shown that when medication is combined with psychotherapy, treatment is more successful with a lower rate of relapse (Blackburn, Eunson, & Bishop, 1986). Alternative medicines that include herbs and acupuncture have grown in popularity, but there are very few reliable outcome studies proving their efficacy. The use of EEG technology has increased the ability to identify neurophysiological differences in people with symptoms of various disorders (John, Prichep, Friedman, & Eastman, 1988; John et al., 2007) suggesting specific functional features that may be modifiable by interventions leading to improved conditions. More specifically, quantitative EEG (QEEG) research has identified neurophysiological indicators in the EEG of increased frontal alpha, increased frontal beta, and increased frontal alpha asymmetry that are associated and correlated with symptoms of depression. Increased relative frontal alpha is associated with dysthymia and generalized depression or unipolar depression, whereas increased relative frontal beta is associated more with a mood disturbance and bipolar symptomology (John et al., 1988).

Research indicates that if depression is not treated, the likelihood of the disorder developing into a chronic lifelong illness is substantial. Studies also indicate that individuals who have had a depressive episode have a 50 to 85% chance of having another during their lifetime (APA, 2000). The statistics are clear and support the need for effective treatment protocols.

AVE has been utilized to help decrease symptoms of premenstrual syndrome, attention deficit disorder, seasonal affective disorder, and migraines (Anderson, 1989; Budzynski, Budzynski, Jordy, Tang, & Claypoole, 1999; Kumano et al., 1996; Manns, Miralles, & Adrian, 1981; Thomas & Siever, 1989). Typically, the mood regulation problems in these disorders improved along with other functional components associated with each of these disorders. The outcome measures used in these studies are based on subject rating scales in which the scores may result from placebo effects with expectations from the treatment paradigm. To date, no quantitative neurophysiological measures have been examined comprehensively to indicate that improved symptoms may be the result of changes made on a neurophysiological level corresponding to improved self-report measures.

This study examined changes in QEEG spectral measures that correspond to the changes in subjective perception of depressive symptom severity following the use of AVE. More specifically, regression analyses was used to determine a possible set of univariate and multivariate measures that can be used as "therapeutic" markers defining AVE therapy for refractory depressed patients.

Objective of the Study

This study utilized AVE at 14 Hz to decrease symptoms of depression and improve associated deviations in QEEG measures reflecting underlying brain dysfunction associated with depressive symptoms. As previously referenced, frontal alpha and beta abnormalities have been associated with depression. Previous studies using this approach trained in the range between 10–18 Hz to impact mood, memory, attention, and arousal (Kennerly, 1994; Kumano

et al., 1996; Lane, Kasian, Owens, & Marsh, 1998; Rosenfeld, 1997, 2000; Von Gizycki et al., 1998). We chose the 14 Hz rate as a frequency midpoint to assist with re-organizing dominant frequency levels.

METHODS

Participants

The study consisted of 16 participants ranging in age from 20 to 67 who were referred by a physician, outpatient mental health center, or self-referral as volunteers for a study on depression. All participants had been previously medicated but were no longer taking medication at the time of the study because the medication either yielded no clinical benefit or resulted in adverse side effects, making compliance extremely difficult. In short, all of these patients were medication nonresponders. All participants were assessed and required to score 15 or higher on the Beck Depression Inventory–II (BDI–II) at baseline, the clinically significant score referenced by the authors of this instrument (Beck, Brown, & Steer, 1996). All participants were required to have increased frontal relative alpha or increased relative frontal beta on a neurometric QEEG evaluation to qualify for the study based on previous studies indicating such deviations in depression samples (John et al., 1988, 2007). Participants were randomly divided into two groups: Group 1 consisted of 6 women and 2 men ranging in age from 20 to 67 ($M = 36.38$ years, $SD = 18.27$), and Group 2 consisted of 5 women and 3 men ranging in age from 42 to 63 ($M = 53.38$, $SD = 6.46$). The difference in age between groups was significant ($F = 6.15$, $p < .03$).

Each participant received 20 AVE sessions at 14 Hz (1 session per day for 5 days each week). During the sham procedure each participant wore photic stimulation goggles with no flashing lights and heard relaxation music on headphones. None of the participants had been exposed to this treatment previously and participants were not informed which of these procedures would yield an expected effect.

Group 1 received AVE every day, 30 min per day, for the first 4 weeks and then received a sham procedure for 4 weeks. Group 2 received a sham procedure for the first 4 weeks and then received AVE treatment for the next 4 weeks. Each participant was administered the Beck Depression Inventory–II (BDI–II) scale and QEEG brain mapping at the beginning of the study, after the first 4 weeks (cross-over), and at the end of the study. Participants were instructed not to consume complex carbohydrates, candy, soda, or caffeine for 1 hr prior to assessment in order to control for the influence of glucose metabolism differences among participants and brain response.

Procedures

Patients were interviewed and required to fill out a medical history form prior to testing.

No participants demonstrated a history of (a) being under the influence of a controlled substance or prescription medication for 24 hr prior to testing, (b) having neurological or other serious (nonpsychiatric) medical disorders at the time or any previous time prior to testing, or (c) bipolar disorder.

Tests

BDI–II. The BDI–II is a 21-item self-report instrument for measuring severity of depression in adolescents and adults 13 years and older. This version of the scale was developed in conjunction with the symptom criteria listed for depression in the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 1994). The BDI–II was developed as an indicator to assess for severity of symptoms and not to clinically diagnose.

Neurometric QEEG measures. QEEG neurometric evaluation was obtained by placing 21 electrodes on the head via an electro-cap consistent with the International 10/20 system. Routine EEG was recorded on a Cadwell Spectrum 32 (Cadwell Laboratories, Kennewick, WA) using a linked-ear montage and with electrodes digitally referenced to the Cz electrode, allowing retrospective montage analysis of all data. Impedences for all electrode

sites on all recordings had 5 K Ohms or less. Data digitization was at a rate of 250 Hz. The amplifier band widths ranged from 0.5 to 30 Hz with the output down at 3 db at these frequencies. Using data gathered under technical conditions as listed above, a total of 40 epochs 2.5 sec in length of EEG were selected and subjected to quantitative analysis of absolute power, relative power, power asymmetry, and coherence. Measurements were logarithmically transformed and referenced to age-adjusted population norms. The following measures were derived for each of four spectral bands (delta [.5–3.5 Hz], theta [3.6–7.5 Hz], alpha [7.6–12.5 Hz], and beta [12.6–25 Hz]) from 19 sites of the 10/20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2): absolute power (calculated as the voltage squared), relative power (calculated as percentage power in each band at each site), power asymmetry (calculated as ratio of powers of all combinations of interhemispheric and intrahemispheric measures as [site1 – site2]/[site1 + site2]), coherence (derived as the ratio of the autospectrum of the spectrum divided by the product of the cross spectrum by the autospectrum for all interhemispheric and intrahemispheric comparisons), mean frequencies within each band, and various multivariate measures that represented combinations of various sites within each of the measurement types (e.g., left lateral relative power delta—represents the combination of delta relative power at T3, F7, C3, T5).

Procedures and AVE Treatment Sessions

The study took place in an outpatient, private practice counseling office. Participants were asked to sit quietly with their eyes closed in a comfortable chair for each session. The treatment room had low lighting and was set up to create a comfortable relaxing environment for the participant during the session. Participants were required to complete pre/posttesting and 20 sessions of AVE. The experimental group received 20 sessions of 14 Hz auditory-visual entrainment and the control group received 20 sessions of a simulated treatment that consisted of eyes closed and relaxation music through headphones. All participants were told that one group would receive the treatment and the other would receive a simulated treatment. Participants were also informed that they would be eligible for the treatment if they were in the control group and it was found to be beneficial. The participants received no medication or counseling during the study treatment phase.

A Mind Gear PR-2x auditory-visual stimulation system (Mind Gear, Inc., Painesville, OH) was utilized to provide the 14 Hz AVE. Green LED glasses were utilized to provide visual stimulation and binaural tones were utilized to provide the auditory stimulation.

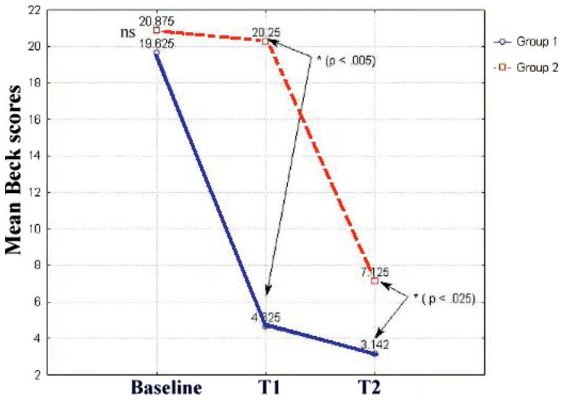
Analysis Procedures

Both the Beck and QEEG measures were measured at three time points: baseline prior to any treatment (Baseline), 4 weeks following the first treatment for each group (T1), and 4 weeks following the second treatment for each group (T2).

To assess the differences in the Beck Scores, nonparametric *t* tests for independent groups were conducted to test for differences between group means at each time point. As all QEEG measures were normalized against health age-matched norms (i.e., *z* scores), only *z*-scored measures were used in analyses. To reduce the number of variables, three models of regression analyses were considered—Forward Regression, Backward Regression, and a stepwise regression model.

To demonstrate that these measures *did not change* significantly during sham procedures, a difference score was derived using the baseline period compared to the period following the sham control. For Group 1, this meant T1 minus T2, and for Group 2, Baseline minus T1. Once difference scores were calculated, the standard deviation for each measure within each group was calculated. A normalized score is then calculated by dividing each measure by the standard deviation for that measure within each group. A mean for the resulting normalized measures was tested using a *t* test for a single sample mean against a mean of zero for each group.

FIGURE 1. Graph showing the change in the mean BDI-II scores at baseline, following treatment phase 1 (T1) and treatment phase 2 (T2) for each of the treatment groups.



RESULTS

Measurement of Depression Symptoms

All participants in this study showed significant changes in BDI–II measures following AVE treatment; in other words, there were no nonresponders. Figure 1 shows scores for the three time points on the BDI–II in this cross-over design.

Nonparametric *t* tests for independent groups were conducted to test for differences between group means at each time point. The results are shown in Table 1. No significant differences between groups were noted at the baseline time point but significant differences were noted at T1 and T2.

Neurometric QEEG Measures

Treatment effect analyses. The forward regression model yielded six variables as shown in Table 2 accounted for 99% of the variance. Backward and stepwise regression models yielded only four variables that accounted for less than 90% of variance, respectively. All variables listed in the resultant backward and stepwise regression models were included in the variable list derived by forward regression, and thus the forward regression model was selected. Figure 2 illustrates these changes for each group.

In sum, these group analyses indicate that *z*-score changes indicating decreased deviation of intrahemispheric beta asymmetry between left fronto-temporal and left temporal regions, an increase of theta mean frequency at the midline frontal pole, a decrease in left temporal alpha mean frequency deviation, a decrease in beta mean frequency for the right parietal region, a significant change in the combined asymmetry measure in frontal regions, a decrease in the bipolar fronto-temporal delta coherence, and mean frequency in the low frequency bands in the right parieto-occipital regions. It is important to note that these changes in mean *z* scores reflect subtle changes across group values that are generally in the ''normal range'' of functioning. To appreciate these changes more fully, a casewise examination of the changes in these variables is demonstrated.

As noted in Figure 3, there is no clearly discernible pattern of changes within or across cases in each group between pretreatment and posttreatment conditions.

Analyses for nontreatment phase. Utilizing the measures derived from regression models that accounted for more than 99% of variance collapsed across both groups, an analyses was needed to demonstrate that these measures *do not change* significantly within each group during the simulated treatment procedures. For each group, a 8×6 matrix of normalized measures were derived by the aforementioned analyses. The *t* test for a

TABLE 1. Kolmogorov-Smirnov test results for Beck Depression means.

	Max Negative Difference	Max Positive Difference	*P*	Group 1 *M*	Group 2 *M*	Group 1 *SD*	Group 2 *SD*	Group 1 Valid *N*	Group 2 Valid *N*
Beck 1	−.25	0.25	>.10	20.875	19.625	7.26	5.26	8	8
Beck 2	.00	0.875	<.005	20.25	4.625	6.67	4.50	8	8
Beck 3	.00	0.75	<.025	7.125	3.142	3.44	1.66	8	8

TABLE 2. Exploratory analysis for a treatment effect with six-variable base model.

	ANOVA of Change in QEEG Measures				
Source	df	Sum of Squares	*M* Square	*F*	*p*
Model	6	523.24	87.207	41.64	<.0001
Error	8	16.76	2.095		
Corrected Total	14	540.00			
Variable	Parameter Estimate	Standard Error	Type II SS	*F*	*p*
Intercept	3.135	0.68	779.07	371.95	<.0001
F8T5BIASY[a]	−1.544	0.83	7.24	3.46	.10
FPzTMF[a]	5.472	0.82	92.52	44.17	<.001
T3AMF[a]	−2.042	1.27	5.43	2.59	.15
P4BMF[a]	−3.718	1.01	28.35	13.54	<.01
FRONTCASY[a]	−4.552	1.92	11.75	5.61	.045
F7T3/F8T4DC-F8T4DCOH[a]	−1.920	0.59	22.55	10.77	.011
	Forward Selection: Step 1[b]				
Source	df	Sum of Squares	*M* Square	*F*	*p*
Model	7	537.24	76.75	194.82	<.0001
Error	7	2.76	0.39		
Corrected Total	14	540.00			
Variable	Parameter Estimate	Standard Error	Type II SS	*F*	*p*
Intercept	12.118	0.34	497.26	1262.24	<.0001
F3T5BIASY[a]	−2.045	0.37	12.05	30.59	.0009
FPzTMF[a]	6.669	0.41	104.40	265.02	<.0001
T3AMF[a]	−1.956	0.55	4.98	12.64	.0093
P4BMF[a]	−6.200	0.60	41.44	105.19	<.0001
FRONCASY[a]	−13.918	1.78	24.12	61.23	.0001
F7T3/F8T4DCOH[a]	−2.045	0.25	25.40	64.48	<.0001
P402ML	6.113	1.03	14.00	35.53	.0006
	Forward Selection: Step 2[c]				
Source	df	Sum of Squares	*M* Square	*F*	*p*
Model	8	539.61	67.452	1050.44	<.0001
Error	6	0.39	0.064		
Corrected Total	14	540.00			
Variable	Parameter Estimate	Standard Error	Type II SS	*F*	*p*
Intercept	11.68	0.16	364.37	5674.36	<.0001
F3/T5BIASY[a]	−2.26	0.15	13.93	216.92	<.0001
FPZTMF[a]	6.47	0.17	94.30	1468.58	<.0001
T3AMF[a]	−1.63	0.23	3.25	50.56	.0004
P4BMF[a]	−6.87	0.27	42.29	658.54	<.0001
FRONTCASY[a]	−14.32	0.72	25.33	394.52	<.0001
F7T3/F8T4DCOH[a]	−1.91	0.11	21.29	331.62	<.0001
P4O2ML	6.55	0.42	15.60	242.99	<.0001
F8OMF	−0.54	0.09	2.37	36.95	.0009

TABLE 2 (continued)

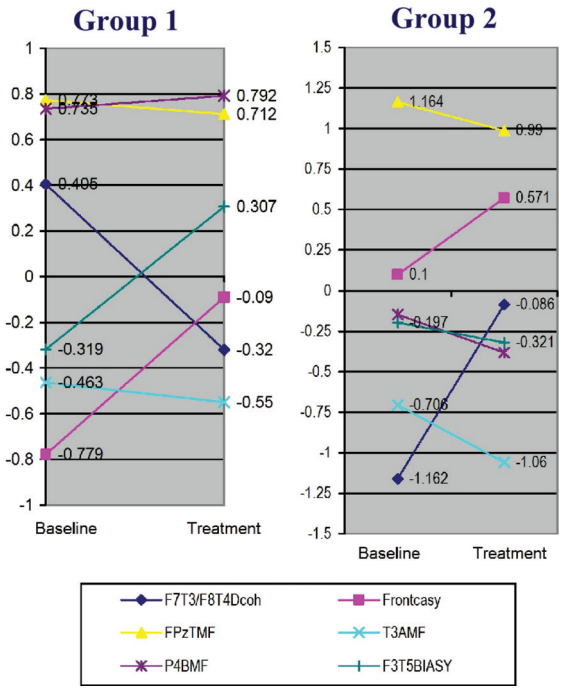
Step	Summary of Forward Selection					
	Variable Entered	Number Vars In	Partial R^2	Model R^2	F	p
1	P4O2ML	7	0.0259	0.99	35.53	.0006
2	F8OMF	8	0.0044	1.00	36.95	.0009

Note. ANOVA = analysis of variance; QEEG = quantitative EEG.
[a]Forced into the model by the INCLUDE = option.
[b]Variable P4O2ML entered: $R^2 = .9949$.
[c]Variable chg536 entered: $R^2 = .9993$.

single sample of the mean normalized measure against a mean of zero was conducted for each group. Thus for Group 1, this meant looking at the difference from treatment time point 1 to treatment time point 2. Table 3 shows the results.

The same analysis was conducted for Group 2. A *t* test for single sample *t* test for the mean normalized measure against a mean of 0 was conducted, which meant that for Group 2, we are looking at the difference from baseline to time point 1. Table 4 shows the results of this analysis.

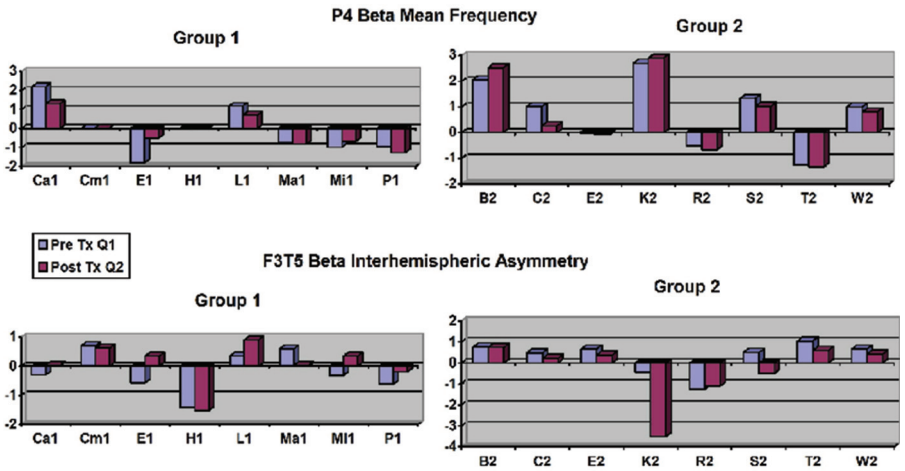
FIGURE 2. Graphs showing the group differences for the mean values for significant QEEG variables related to changes with AVE therapy.



DISCUSSION

The findings from this study support the findings from previous studies in identifying the role of the frontal and temporal region involvement in the regulation of mood regulation. Behavioral data demonstrated a significant change in depressive mood status in two groups of patients previously identified as medication failures. It is doubtful that the effects of the AVE treatment used in the study was the result of a "placebo effect" because patients were blind to which procedure was expected to yield and improved clinical condition. This study has shown that significant changes in brain function took place only following the administration of the specific AVE protocol used in the study as no significant changes in the identified brain regions were associated with mood regulation change when comparing their status from a baseline to a sham procedure. Although the regions involved significantly changed with the treatment explored in the paradigm, the directionality of change is not uniform. In a comparison of the changes in key variables established from the regression models used for the mean values in each group or when examining the changes on a casewise basis, there was no consistent pattern defining the "normalizing" process when reviewing the changes in these variables. The case-by-case individual differences that appeared to be present may be accounted by other differences between participants pertaining to other psychological capabilities or deficiencies. For example, individuals may have problems with memory, attention, and so on. Alternatively, the idea that refractory depressed patients should show slightly

FIGURE 3. Graphs showing casewise Z-score values for each group for QEEG variables corresponding to changes induced with AVE therapy.



different changes in the key measures noted in the study suggests that there may be a complex ''balance'' in brain activity that needs to be achieved for improved clinical outcome, more so than simply improving one primary deviant band of activity in these regions, for example, increased relative frontal alpha or increased relative frontal beta. Thus, examination of univariate features of the neurometric QEEG cannot necessarily predict or define cases of refractory depressed patients. The regression analysis by itsnature partialing out their intercorrelations and by inclusion of a multivariate variable (frontal alpha asymmetry) indicates a complex dynamic of activity and possible respective neurotransmitter systems involved in these regions in the brain that may be contributing to depression symptoms that are not always predictably treatable by psychotropic medications (Saletu, Anderer, & Saletu-Zyhlarz, 2006).

Further analyses to examine other ''effects'' of AVE therapy need to be considered. For example, by driving the brain to a specific frequency in the entraining process, there may be some form of resetting mechanism across

TABLE 3. Analysis of difference from T1 to T2: Group 1.

	Test of Means Against Reference Constant (Value) (Subset Group 1)							
	M	*SD*	*N*	*SE*	Reference Constant	*t*	*df*	*p*
M six variables	−.198	.402	8	0.142	0.00	−1.39	7	.206

Note. T1 = 4 weeks following the first treatment; T2 = 4 weeks following the second treatment.

TABLE 4. Analysis of difference from T1 to T2: Group 2.

	Test of Means Against Reference Constant (Value) (Subset Group 2)							
	M	*SD*	*N*	*SE*	Reference Constant	*t*	*df*	*p*
M six variables	−.160	.374	8	0.132	0.00	1.21	7	.265

Note. T1 = 4 weeks following the first treatment; T2 = 4 weeks following the second treatment.

brain regions that enables brain dynamics to function more optimally (Thatcher, North, & Biver, 2008). Further, source localization techniques such as LORETA may prove to yield common source localized functional changes in common subcortical structures that may be involved in these cases in the treatment process. Future research is also needed to explore "tweaking" AVE therapies by keying on maximal deviations in the narrow bands on an individual basis. Such increased specificity of the training frequency to the individual patient may yield improved changes in shorter treatment periods and/or an increased likelihood to yield significant clinical outcomes in larger clinical cohorts to be examined.

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