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INTERMITTENT BURST-FIRING WEAK (1 MICROTESLA) MAGNETIC FIELDS REDUCE PSYCHOMETRIC DEPRESSION IN PATIENTS WHO SUSTAINED CLOSED HEAD INJURIES: A REPLICATION AND ELECTROENCEPHALOGRAPHIC VALIDATION[1]

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Summary.—14 patients who reported chronic depression more than one year after closed head injuries were exposed to weak (1 microTesla), burst-firing magnetic fields either across the temporal lobes or over the left frontal lobe. The treatment was for 30 min. once per week for 6 wk. The reduction in depression scores after 5 wk. of treatments and after 6 wk. of no treatment (follow-up) accommodated 54% of the variance for both groups. The changes in depression scores did not differ significantly between the two groups (temporal vs frontal). Following treatment, the frequency of complex partial epileptic-like experiences decreased significantly only for the 7 who received the bilateral stimulation over the temporal lobes. Quantitative bipolar electroencephalographic measurements over the occipital, prefrontal, and temporal regions showed increased power within the 16-Hz to 18-Hz range 6 wk. after termination of treatment for those 7 patients who received the burst-firing magnetic fields bilaterally over the temporal lobes but not over the left prefrontal region.

Whereas Transcranial Magnetic Stimulation (TMS) involves focal applications of very strong (1 Tesla) simply shaped magnetic fields over the skull (Wassermann & Lisanby, 2001), transcerebral magnetic (TCM) field treatments involve the applications of temporally complex magnetic fields at field strengths about one million times less intense. Baker-Price and Persinger (1996) reported that six weekly applications of a burst-firing magnetic field (1 microT) across the temporal lobes significantly reduced the psychometric depression of patients who had sustained closed head injuries. The effect size of applying the burst-firing field, whose structure was derived from the firing pattern of amygdaloid neurons, was similar to that reported for Transcranial Magnetic Stimulation. More recent studies involving normal volunteers indicated that bitemporal application of this field once per week for three weeks, but not for three consecutive days, elevated mood (Tsang, Persinger, & Koren, 2002) in normal volunteers.

The present study was designed to discern if transcerebral stimulation with the effective burst-firing magnetic fields over the left prefrontal region

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would be as potent as the application bilaterally over the temporal lobes. We selected the left prefrontal region for comparison because the major cerebral correlates of clinical depression are hypofunction within the prefrontal regions (Pearlson & Schlaepfer, 1995; Videbech, 2000). Application of repetitive transcranial stimulation (rTMS) over the left prefrontal region has been associated with increases in regional cerebral blood flow (Speer, Kimbrell, Wassermann, Repella, Willis, Herscovitch, & Post, 2000).

Over the years more than half of all of the patients we have assessed (approximately 1,000) who were depressed and reported pain during the years following "mild" brain injuries had not responded to antidepressant medications prescribed by their family physicians or psychiatrists. We suspect the refractory profile may reflect the procedures by which antidepressant medications are selected. Drugs developed for marketing are usually based on the results of clinical trials involving patients whose depression was secondary to sociogenic (loss of a loved one, ontogenetic progression) or endogenous sources.

Our hypothesis has been that a substantial proportion of patients who experience depression and pain subsequent to a closed head injury (with or without loss of consciousness) do not respond to antidepressant medications because the symptoms are due to elevated metabolic and electrical activity within the mesiobasal (hippocampus and amygdala) portions of the temporal lobes rather than a generalized decreased metabolic activity within the (particularly left) prefrontal lobes. However, the clinical manifestations of this "dominating" limbic effect upon even a normal prefrontal function would be similar to "hypofunction." We (Bureau & Persinger, 1995) had found that the incidence of limbic motor seizures in rats had been reduced following 20 pairings of subclinical dosages of lithium and pilocarpine with the same burst-firing pattern as that employed in the present study.

On the basis of our previous study (Baker-Price & Persinger, 1996) and the anticipated effect size of the treatment, we reasoned that a sample of 14 patients (seven per group) would be sufficient for any differences between applications of the fields over the temporal lobes or left prefrontal lobe to achieve statistical significance with an effect size that would be practical for clinical application. For humane reasons we decided before the experiment to reduce our probability of obtaining statistical significance but to increase the likelihood of benefit to the patients by not including a sham-field group. Consequently, the focus of the study was based on the potentially greater effectiveness of one site of application of the field compared to the other.

Method

Subjects

A total of 14 male and female patients (ages 25 through 45 years) who had experienced chronic depression (that did not respond to antidepressants) following a closed head injury were referred for treatment by local professionals or volunteered in response to a published notice in a local newspaper. Four of the subjects reported they experienced a cessation of consciousness following the mechanical impact. The average time between the brain trauma and the testing was two years. Seven of the patients were randomly assigned to receiving the same treatment reported by Baker-Price and Persinger (1996) across the temporal lobes while another seven received the same magnetic field patterns over the left prefrontal region.

Procedure

The basic design involved meeting the patient once per week for 6 wk. (six sessions). The protocol had been approved by the university's Human Ethics Committee, and the volunteers signed informed consents that emphasized they could discontinue the treatment at any time. Because our goal was to produce permanent rather than postsessional improvements, the psychometric tests and electroencephalographic measurements were completed at the beginning of a session before the transcerebral application of the 1 microTesla magnetic fields. After the end of the sixth session the patient did not return for measurements and was not contacted by the clinician (first author), except for a reminder of the follow-up session, until six weeks had elapsed. At that time final measurements were collected. Each subject was then given a brief report of progress.

At the beginning of each week (before the transcerebral magnetic field treatment) and 6 wk. after the final treatment (follow-up), each subject completed the Beck Depression Inventory (Beck & Steer, 1987). At the beginning of the first week, at the last treatment (6 wk. later), and 6 wk. after that the person completed Roberts' questionnaire for the Epileptic Spectrum Disorder (Roberts, Varney, Hulbert, Richardson, Springer, Sheperd, Swan, Legrand, Harvey, & Stuchen, 1990). During the 6 wk. of the treatment three of the subjects who had been receiving the left prefrontal treatment did not return for the last two or three sessions.

At Session 1 (baseline), Session 6 (after five treatments), and Session 7 (6 wk. follow-up, after 6 wk. of no treatment or contact with the clinician), silver electrodes were attached by EC2 electrode cream over the frontal (F7, F8), temporal (T3, T4), and occipital (O1, O2) lobes. Once the canisters were attached, bipolar activity was recorded (filter set at 10 Hz) for 10 min. by a P79 Grass electroencephalographic instrument. The canisters containing the solenoids were then held by Velcro over either the temporal lobes or the left frontal region. Electroencephalographic measurements were completed for 10 min. while the fields were not activated.

During the treatment the patient sat within a comfortable chair that was housed in a darkened acoustic chamber. The fields were delivered through two small canisters (each containing four small solenoids) through which a burst-firing magnetic field was presented once every 3 sec. for 30 min. once per week for 6 wk. The point duration for each of the 259 values that composed the burst-firing (see Persinger, Tiller, & Koren, 2000 for a pictorial representation) was 3 msec. The configuration of the circuit was such that the fields were generated between the pairs of solenoids and the burst-firing pattern was rotated to each homologous pair of solenoids (one in each canister) every 0.5 sec. (1 cycle = 2 sec.).

The records for each of the three channels were later examined for dominant frequency in the following manner. A ruler was placed along the record at the midpoint between the peaks and troughs. The numbers of excursions more than one-third above the midline of the activity of the pen recordings were recorded manually by the first author for each second of the 600 successive (10-min.) readings).

For each subject the numbers of seconds in which appeared specific 1-Hz frequency increments, between 9 Hz and 27 Hz, were counted for each channel (occipital, temporal, frontal) for each subject for the three sessions. Multivariate analyses of variance were completed for each of these sets of 1-Hz increments of frequencies as a function of the session (baseline, 6 wk. after treatment, and 6 wk. after cessation of treatment) and the application position of the solenoids: bilateral temporal lobes versus left prefrontal region.

To extract a variant of "power" for each frequency, the total numbers of seconds containing each 1-Hz increment for each session was divided by the total numbers of seconds counted for that session, for each channel. This calculation also minimized the excessive contribution from any single subject. Two-way analyses of variance, with one level repeated (session) and one between-groups treatment (position of magnetic field) were also completed for each of the 19 1-Hz frequency bands. All analyses involved SPSS software on a VAX computer.

Results

Two-way analysis of variance with one level repeated (first measure, sixth measure) and one between-subject factor (left prefrontal vs bilateral) for the Beck Depression scores showed no significant difference between the region of application of the field ($F_{1,9} = .11$, $p > .05$) but a significant difference over the time of the treatment ($F_{1,9} = 10.37$, $p < .01$; $\eta^2 = 53\%$ of the variance); the interaction between application geometry and sessions was not statistically significant. The means and standard deviations for the first and second Beck Depression scores were 19.7 ($SD = 8.6$) and 14.1 ($SD = 5.2$), respectively. The *M* and *SD* for the scores at follow-up were 15.1 ($SD = 7.6$).

Post hoc analysis using t tests for correlated data indicated that the depression scores were significantly lower after the five treatments (Week 6) and 6 wk. after no treatment (the follow-up) than the baseline levels.

Although the results of the analyses with the complex partial epileptic-like signs were not significant statistically with the full analyses, the seven patients who had received the 6 wk. of treatment with the bilateral fields showed significantly ($F_{1,9}=8.91$, $p=.01$; ω^2 estimate = 48% of variance explained) less frequent signs ($M=2.0$, $SD=1.1$) than those who received the left prefrontal treatment ($M=4.8$, $SD=1.9$). These group differences were not present ($M=4.6$, $SD=3.3$; $M=5.3$, $SD=2.7$, respectively) before the treatment began. At the time of the 6-wk. follow-up the scores for the patients who received the frontal and temporal treatments were $M=2.1$ ($SD=1.6$) and $M=4.0$ ($SD=1.8$), respectively. The results are also shown in Fig. 1 (insert). Covariance for the concomitant depression scores before the analyses did not change the strength of the group difference ($F_{1,8}=6.37$, $p<.05$; $\eta^2=$ 41% of the variance explained).

The results of the two-way analysis of variance for the numbers of seconds containing the various 1-Hz bands of activity yielded no statistically

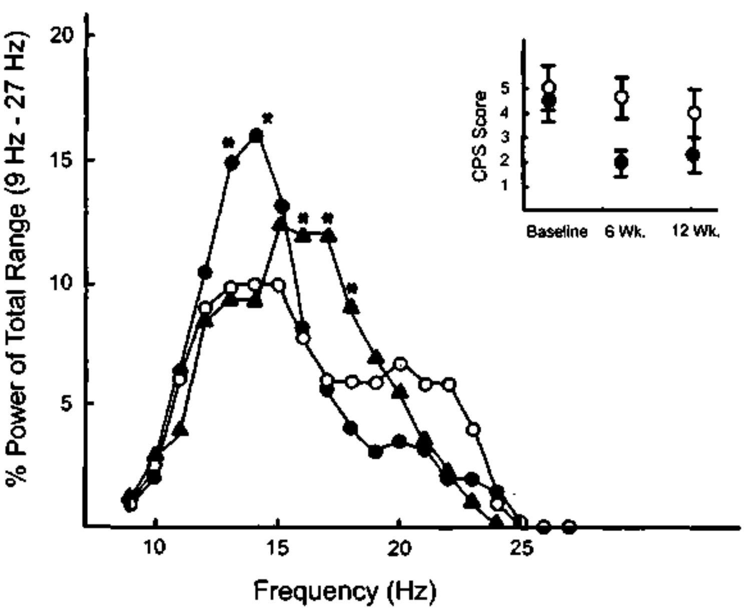

FIG. 1. Percentages of power within 1-Hz frequency increments between 9 Hz and 27 Hz over the temporal lobes during baseline (○), after 6 wk. of treatments (●), and after 6 wk. of no treatment (12 wk. follow-up) (▲). Inset: mean score for complex partial epileptic-like signs for patients who received the burst-firing magnetic fields either over both temporal (●, $n=7$) lobes and only the left prefrontal (○, $n=4$) region.

significant differences between the groups who received the two field applications ($Fs_{1,9} < 1.00$) and no statistically significant interactions ($F_{2,18} < 1.00$) between session and the position of the applied magnetic field.

For the "power measurements," two-way analyses of variance with one level repeated (baseline, 6 wk. later, 12 wk. later) and one not repeated showed statistically ($p < .05$) significant (all $dfs = 2,20$) differences between sessions (η^2 estimates in parentheses) for the 13-Hz ($\eta^2 = 23\%$), 14-Hz ($\eta^2 = 41\%$), 17-Hz ($\eta^2 = 30\%$), 18-Hz ($\eta^2 = 23\%$), and 19-Hz ($\eta^2 = 20\%$) bands only.

The results are shown in Fig. 1. *Post hoc* analyses indicated statistically significant increases in the percentages of activity over the temporal lobes only within the 13-Hz to 14-Hz bands for both prefrontal and bitemporal treatments following the five treatments compared to the baseline measurements and the measurements 6 wk. after the termination of treatment. On the other hand, the significant differences in the percentages of activity within the 17-Hz to 19-Hz band over all three lobes was primarily due to the elevated amount of activity in this range during the follow-up period after 6 wk. of no treatment for the patients who received the bitemporal magnetic fields compared to those who received the fields applied over the left prefrontal region. The measures for this range of activity did not differ significantly between groups for the baseline or after 6 wk.

To discern if the changes in scores for the complex partial epileptic-like signs and the Beck Depression Inventory were quantitatively associated with the electroencephalographic scores, Spearman *rho* correlations were calculated between the measures of power for the 13-Hz and 14-Hz band (Fig. 1) over the temporal lobe after 6 wk. of treatment and for the measures of power for the 17-Hz, 18-Hz, and 19-Hz band (Fig. 2) recorded during the follow-up. Values of Spearman *rho* were significant between the severity of depression (Beck scores) before treatment and the amount of power in the 12-Hz (.64, $p < .05$), but not for 13-Hz (.52, ns), and 14-Hz (.53, ns) bands.

These values for the association between the power measures for these increments and the depression scores after 6 wk. of treatment were –.38, –.42, and –.27, respectively (ns). The *rho* coefficients between the scores for complex partial signs for the subjects who received the treatment over the temporal lobes only and the significant bands measured during the follow-up were 16 Hz (.03), 17 Hz (–.61, $p = .07$), 18 Hz (–.40, ns), and 19 Hz (–.85, $p < .01$). There were no significant correlations between the psychometric scores during the follow-up and the power for any 1-Hz band except for 18 Hz ($rho = .74$, $p = .02$).

Discussion

The psychometric results of this study replicated those reported by Bak-

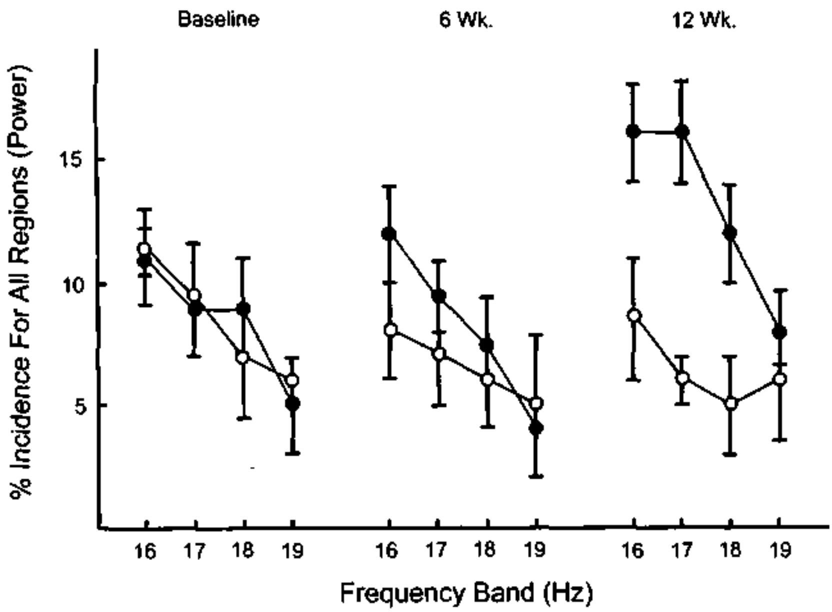

FIG. 2. Percentage of transcerebral power (frontal, temporal, and occipital) within the 1-Hz increments between 16 Hz and 19 Hz during baseline, after 6 wk. of treatment, and after 6 wk. of no treatment (12 wk. follow-up) for patients who received the treatment over the left frontal (o) or bilateral temporal (●) region.

er-Price and Persinger (1996). Subjects who were exposed to the treatment showed a significant reduction in depression by Week 6 after five 30-min. exposures to the burst-firing magnetic fields. The treatment accommodated more than 50% of the variance in the psychometric measures.

We also found that exposure to treatment was followed by significant decreases in the weekly incidence of complex partial epileptic-like experiences. Like the Beck Depression scores, the attenuation of complex partial epileptic-like signs was still evident when the subjects returned for testing 6 wk. later after 6 wk. of no treatment.

There were no statistically significant differences in the depression scores for the patients who received the applications of the burst-firing magnetic fields across the temporal lobes versus the left prefrontal regions. However, there was a statistically significant interaction between the frequency of the complex partial epileptic-like experiences and the position of the applied fields. Those subjects who received the bilateral temporal applications showed a conspicuous reduction in the frequencies of these experiences after five treatments, and this was still evident even after six weeks of no treatment. This reduction did not occur for the four patients who received the prefrontal applications.

For humane reasons we decided not to run a sham-field group in the present study. Instead, we compared the application geometry of the fields. We assumed that, if the bitemporal magnetic fields were most potent, their effects should still be evident and statistically significant even when compared with the left prefrontal application. Although this approach would reduce the *size* of the effect of the magnetic field treatment (relative to the inclusion of a sham-field group), as clinicians we felt that the patients receiving the prefrontal applications would at least have some relief. All of these patients had been treated by psychiatrists or physicians without relief. Many of these patients were experiencing the type of futility that precedes self-destructive behaviors. It is interesting that three of the patients who had been randomly assigned to the prefrontal arrangement did not complete the study. This may suggest that the treatment was not beneficial. That issue needs study.

Two electroencephalographic results were notable in this study. The first involved a significant increase in the relative power of frequencies between 16 Hz and 19 Hz following bitemporal treatments but not prefrontal treatments. This increase did not appear until the follow-up. If this increase is considered in context of the reduction in complex partial epileptic-like signs that occurred by the end of the treatment and was still evident during the follow-up examination, then it is possible that this treatment increased the percentage of cerebral activity within the low beta range.

Tebano, Cameroni, Gallozzi, Loizzo, Palazzino, Pezzini, and Ricci (1988) reported that patients who sustained mild to moderate head injury 3 to 10 days before the measurements showed a reduction in the mean power for fast beta activity (20 Hz to 36 Hz) and fast alpha activity (10.5 Hz to 13.5 Hz) but an increase in the mean power of slow alpha (8 Hz to 10 Hz). This effect was noted whether the patient had or had not sustained a suspension of consciousness. In the present study application of the burst-firing magnetic fields over either the prefrontal or the temporal lobes increased the "power" within the 13-Hz to 14-Hz band over the temporal lobes.

Because the increase in power within the 13-Hz to 14-Hz band over the temporal lobes occurred for both groups, we cannot exclude the possibility that some nonspecific factor may have been responsible for the improvement. However, the increase in power within the 17-Hz to 19-Hz range was specific to the patients who received the application of the fields across both temporal lobes but not over the left prefrontal lobe. That this effect was an artifact of field application is not possible because the electroencephalographic measurements were not taken at the time of the field application. That this increase was due to entrainment is unlikely. Spectral analyses (fast Fourier transform) of the burst-firing pattern directly from the software that generated the magnetic field showed primary peaks around 29 Hz, 33 Hz, and 42 Hz.

There were smaller peaks in the spectral power of the burst-firing field around 14 Hz to 15 Hz and 18 Hz to 19 Hz. One cannot exclude the possibility that between the first and the sixth sessions permanent modifications occurred within aggregates of neurons mediating the specific cortical frequencies reflected in electroencephalographic activity. Zhongqi, Gang, Cuiyun, Zhiuan, Guozhen, Yan, Yao, and Shaozhang (1998) have shown that 16-Hz electromagnetic fields but neither 3-Hz nor 31-Hz magnetic fields within a specific intensity window can significantly affect the influx of calcium ions within cerebral tissue. If this assumption be correct, then treatment may have facilitated the learning, which is defined as the more or less permanent change in behavior with experience of less clinical and more adaptable behaviors.

The interstimulus interval between treatments by bitemporal application of the burst-firing magnetic fields may be critical. An intuitive decision to increase the frequency of applications, for example, to daily treatments, may not be optimal. Tsang, *et al.* (2002) exposed normal volunteers to the same complex magnetic field employed in the present study. Relative to sham-field applications, the burst-firing applications reduced scores for psychometric depression only when applied for 30 min. once per week for 3 wk. Applications for 30 min. per day for three successive days were not effective.

With respect to efficacy the temporal structures of complex magnetic fields can be considered similar to the spatial (molecular) structures of pharmacological agents. The temporal relationship of the duration of the field with the interstimulus interval for the application of complex magnetic fields might be considered comparable to the dosage of a drug. Pharmacological wisdom clearly shows that an optimal effect with a particular dosage of an antidepressant or anxiolytic compound does not always increase simply by increasing the amount of drug. In fact, for some psychotropic drugs, particularly antidepressants and anxiolytics, larger amounts may eliminate improvements. The optimal prophylaxis of some anticoagulant drugs, such as aspirin, may only require consumption once per week.

A similar "optimal dosage" manifested as "optimal intervals" of interstimulus exposures, may occur for transcerebral stimulation by weak complex magnetic fields. It would be analogous to the powerful differences between massed-practice vs spaced-practice for some types of learning. More permanent changes in behavior are favoured by spaced-practice relative to massed-practice.

That the response of the brain to electrical stimulation is strongly influenced by the interstimulus interval has been shown for kindling. According to Goddard, Dragunow, Maru, and Macleod (1986), kindling from the amygdala did not occur with interstimulus intervals of 5 or 10 min. but required intervals between 20 min. and 60 min. Assuming a functional impact of 10 sec. from a single kindling stimulus, the ratios for the stimulus duration divided by the interstimulus interval would be .04, .02, respectively, for the ineffective procedures and .008 and .003, respectively, for the effective procedures.

The duration of our exposures has been about 30 min. For daily treatments, the ratio for this stimulus duration divided by the interstimulus interval would be about .02. For weekly treatments, these ratios would be about .004. If there be some "scale invariance" for the impacts of electromagnetic fields within the brain, similar to Weber's law, then isolation of the interstimulus interval may be essential to elicit optimal clinical effects.

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