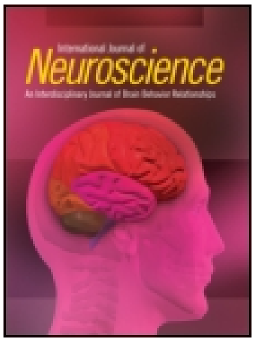

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International Journal of Neuroscience

ISSN: 0020-7454 (Print) 1543-5245 (Online) Journal homepage: https://www.tandfonline.com/loi/ines20

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To cite this article: L. J. MARTIN, S. A. KOREN & M. A. PERSINGER (2004) INFLUENCE OF A COMPLEX MAGNETIC FIELD APPLICATION IN RATS UPON THERMAL NOCICEPTIVE THRESHOLDS: THE IMPORTANCE OF POLARITY AND TIMING, International Journal of Neuroscience, 114:10, 1259-1276, DOI: 10.1080/00207450490475689

To link to this article: https://doi.org/10.1080/00207450490475689

Published online: 07 Jul 2009.

Intern. J. Neuroscience, 114:1259–1276, 2004

ISSN: 0020-7454 / 1543-5245 online
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INFLUENCE OF A COMPLEX MAGNETIC FIELD APPLICATION IN RATS UPON THERMAL NOCICEPTIVE THRESHOLDS: THE IMPORTANCE OF POLARITY AND TIMING

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The application of a weak (1 microTesla) complex magnetic field pattern with a relevant electrophysiological signature produced an analgesic response in rats to thermal stimuli when the pattern was presented once every 4 sec for 30 min through iron-core solenoids. In one experiment, the burst-firing pattern was presented once every 4 s for 30 min and restricted to the positive polarity, negative polarity or a bipolar equivalent. The strongest analgesia occurred when the burst-firing pattern was presented with positive polarity or as the typical bipolar signal. Administrations of the burst-firing pattern once per week for four consecutive weeks produced analgesia that was clearly evident during the first, third, and fourth weeks but not during the second week of treatment. A telephone sensor coil (that can be readily obtained from local electronic shops) was then used instead of the solenoids along with an audio (.wav) file to generate the magnetic field; the analgesia was still apparent. However, when the magnetic pattern was generated

Received 21 November 2003.
Portions of this research were supported by contributions by Chin-Ning Chu and Curt Paulson from NeuroScience Industries. E-mail: cnc@strategic.org
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from a compact disc source the analgesia was not evoked. The current results suggest that these fields can be generated through simple commercial devices controlled by available computer software.

Keywords computer sound card files, magnetic fields, pain analgesia

The experience of pain is the most commonly reported ailment among the clinical population. The removal of pain from the general population has been a primary goal of clinicians and general practitioners who have usually employed conventional (i.e., pharmacotherapy) or alternative means (i.e., herbal remedies). One alternative method for treating the experience of pain is the use of magnetism. The idea of using magnetism to alleviate pain is far from novel. The ancient Chinese and Incan civilizations used lodestones to combat a variety of medical issues.

More recently the use of the static magnetic field has been demonstrated to reduce the pain associated with diabetic neuropathy (Weintraub, 2003), lower back problems (Holcomb et al., 2003), and post-polio complications (Hazlewood, 2003). Earlier work by Sandyk (1992) demonstrated that a 5 Hz externally applied magnetic field in the picoTesla range partially reduced the neuralgic pain and headaches that were associated with multiple sclerosis (MS). This treatment also rapidly resolved an acute relapse of MS.

In pharmacology the spatial structure of the drug determines binding affinity to receptor subtypes and ligand activation and thus its biological and behavioral effects. In magnetic field research the temporal structure or the structure of the pattern over time is critical for eliciting desired effects. The authors (Martin & Persinger, 2003) have hypothesized that the use of a static magnetic field in magneto-therapy is analogous to using a simply structured molecule in pharmacology (i.e., saline or water). In essence the static field is redundant and therefore simple in structure. Therefore the use of magnetic fields with intrinsically complex temporal structures resembling electrophysiological patterns would be optimal for targeting specific behavioral processes (i.e., pain or learning and memory).

In humans intermittent burst-firing (resembling amygdaloid activity) weak (1 microTesla) magnetic fields reduced psychometric depression in patients who sustained closed head injuries (Baker-Price & Persinger, 1996, 2003). Each subject was treated with the burst-firing magnetic field for 30 min once a week for 6 weeks. Fleming et al. (1994) and Martin et al. (in press) have reported that the same burst-firing pulse elicited a consistent analgesic response in rats when each presentation of the burst-firing magnetic pattern was separated by 4 s and each point within the pattern was presented for 3 ms. The authors (Martin & Persinger, 2003) have also demonstrated that the application of a specific complex magnetic pattern based on frequency-modulated principles also elicited a heightened analgesic response in male Wistar rats. The analgesic responses attained by both magnetic patterns were equivalent to a clinically effective dosage of at least 4 mg/kg of morphine (i.p.).

The patterns of the complex magnetic fields are typically generated by first creating a file that contains a column of numbers. Each number ranges between 0 and 255 such that any value below 127 is negative polarity and any value above 127 is positive polarity. When the sequential order of the numbers is displayed along the horizontal axis and the values between 0 and 255 are displayed along the vertical axis, the shape or "pattern" can be clearly visualized. The numbers in the file are transformed to increments of specific voltage between –5 V and +5 V by a custom made digital-to-analogue converter (DAC). The converter is accessed through a parallel port (output) from the computer. Two solenoids are connected so the magnetic field is generated between them.

The structure of the burst-firing field traverses both positive and negative polarities when the pattern is visualized from the numbers ranging from 0 to 255. There is some concern that the analgesic effects may be mediated from the dual polarity and not the pattern itself. McKay et al. (2000) showed that applications of a uni-polar (positive polarity) theta burst-magnetic pulse evoked learning deficits for hippocampal dependent tasks. Our present goal was to discern if the same pattern presented as a negative or as a positive polarity would produce analgesia similar to the frequently replicated bipolar effects.

Another obvious issue is the application of the treatment to periods commensurate with clinical practice. The present series of studies examined the effects of weekly exposures (as many clinical treatments are administered) to the complex magnetic pattern. The problem of accessibility to specialized equipment for the treatment was also addressed by transforming the complex waveform into audio files (.wav and .mp3) and by generating the .wav file through a compact disc (CD) or sound card.

In some experiments we substituted the traditional solenoids with a telephone induction coil. It was available commercially (Radio Shack) to record telephone conversations. If the effects were comparable to those previously obtained with the DAC systems and with the solenoids then theoretically a patient can obtain these effects in the home setting with the appropriate audio file and output device (i.e., CD player).

MATERIALS AND METHODS

Subjects

Male (n = 80) albino Wistar rats, between 6 and 12 months of age were employed as subjects. They had been obtained from Charles River (Quebec) and had been habituated to a 12:12 L:D cycle (onset between 0700 h to 0800 h) within temperature-controlled rooms (20 to 22°C) for at least one month before the initiation of the experiments. Rats were monitored daily by experienced Animal Care Technicians. Purina rat chow and water were available *ad libitum.* The rats were maintained, usually 3 per cage, in standard wire cages (40 cm × 24 cm by 18 cm, high) in racks.

General Procedure

All protocols had been reviewed by the university's Animal Care Committee. All rats were treated according to the guidelines of the Canadian Council on Animal Care. All 5 experiments involved essentially the same procedure. Nociceptive thresholds were tested by removing each rat from its home cage and by placing the rat on an Omnitech thermal plate that was maintained at 55°C. The plate was enclosed within a plastic box (18 cm high) so that the rat could not escape. When the rat was placed on the surface (26 cm × 26 cm) of the plate, a foot pedal was depressed to initiate an electronic timing device. Once the rat was observed to lick one of the hind feet twice in any combination, the rat was removed immediately from the apparatus. The elapsed time was automatically recorded. If the rat had not displayed the criterion response by 60 s it was removed.

The first placement on the hot plate was called Trial 1 or the baseline trial. Immediately after the baseline trial the rat was placed within the experimental apparatus that generated the magnetic fields. All exposures to the magnetic field treatment were 30 min in duration with 4 s between each presentation of the burst-firing pattern and each point was presented for 3 ms. These parameters and the graphic structure of the pattern have been published elsewhere (Fleming et al., 1994; Martin et al., in press). Essentially the pattern is composed of 230 points. Each value between 0 and 255 is transformed by a custom-made digital-to-analogue (DAC) converter to gradations between –5 V and +5 V.

The changing voltages were delivered to two solenoids. They were composed of 2 iron nails (each 1 cm in diameter and 25 cm long) wrapped with 1050 turns of 20 gauge insulated wire and separated by about 25 cm. The magnetic fields were generated between the two resulting "poles" that opposed each side of the exposure cage. The intensity of the field most proximal to the poles was 2.5 microT. At distances of 4 cm, 6 cm, 8 cm, and 10 cm from either the pole the values were 1.7 microT, 1.0 microT, 0.5 microT, and 0.3 microT. Along the periphery of the 25 cm × 25 cm × 25 cm plastic box within which the rat was contained the field strengths ranged between 0.1 microT to 0.7 microT. The linear axis of the two solenoids was about 4.5 cm above the cage's surface.

After the 30 min of exposure the rats were tested immediately for thermal response times on the same apparatus (Trial 2). The rats were then returned to their home cages for an additional 30 min. After the interval (60 min since the onset of a treatment and 30 min after the cessation of the treatment) the rats' response latencies were measured for the third time (Trial 3). Our rationale for designing the protocol in this fashion was to investigate the time course of the effects. Smaller time intervals were not chosen (i.e., testing occurring after 10 or 15 min) to minimize the learning phenomenon that may occur with repeated exposure to the hotplate. For all experiments, this procedure was repeated over two successive days, unless specified.

Experiment 1: Effects of Polarity of the Magnetic Pattern

The burst-firing magnetic pattern used by Fleming et al. (1994) was designed to contain both positive and negative polarity components. In this first experiment the burst-firing magnetic pattern was restricted to the positive polarity (n = 4) or the negative polarity (n = 4). A bipolar burst-firing magnetic pattern group (n = 4) and a sham field condition (n = 4) were included for reference purposes. All magnetic field conditions were intensity matched, since the positive and negative polarity pulses were weaker (by one-half) in intensity than the bipolar pulse.

Experiment 2: Weekly Exposures to the Burst-Firing Magnetic Field

Rats were exposed to either the burst-firing magnetic field treatment for only *one* day once per week for four weeks (n = 8) or to sham field conditions (n = 8). The testing on each week occurred for three trials (baseline, trial 2 and trial 3).

Experiment 3: Generating the Magnetic Field Through Telephone Sensor Coils

After baseline measurements, rats were randomly assigned to either the burst-firing exposure (n = 11) or the sham field condition (n = 11). The solenoids were disconnected from the digital to analogue converter (DAC) and were temporarily replaced with a simple cable system (i.e., telephone "pickup," RadioShack 44-533B that was designed to be an induction coil) that can be readily obtained from local electronic shops. The suction cups of the coils were placed on the sides of the cage in the same positions the two solenoids had occupied. The pickup coils were then plugged into the DAC and the magnetic field was generated within the exposure volume. The maximum field strengths in the plane between the two pickup coils when the burst-firing field was generated were 2 microT, 1.5 microT, 0.7 microT, 0.4 microT, and 0.25 microT at distances of 2 cm, 4 cm, 6 cm, 8 cm, and 10 cm, respectively from either coil. The field strength within the majority of the exposure volume was 0.2 microT (2 milligauss).

Experiment 4: Comparing Digital-To-Analogue vs .wave Files for Analgesia

This experiment tested the hypothesis that these analgesic effects could be elicited by the magnetic field after it was converted into a .wav file and generated by a sound card on a personal computer. The authors' rationale was that in this technological era a .wav sound file and a sound card on a personal computer would be more accessible than a custom-constructed digital-to-analogue converter. Rats were exposed to either the burst-firing magnetic pattern generated as an audio file (.wav) (n = 6) through the telephone pickup coils or to the sham field. When the burst-firing pattern was generated by the .wav file, the field strengths at 2 cm, 6 cm, 8 cm, and 10 cm within the plane from either pickup coil was 2 microT, 1.3 microT, 0.6 microT, 0.1 microT, and 70 nT, respectively. The latter intensity (0.7 mG) dominated the volume of the exposure area.

Experiment 5: Generating Burst-Firing Patterns from an Audio CD

Based on the results of the previous experiment, we tested the analgesic effects of the magnetic pattern transformed into an .mp3 format, burned onto a compact disc (CD) and generated using the CD player program on a personal computer. Each condition (burst-firing and sham) had 7 animals per group. The CD was accurately arranged so that it produced the burst-firing magnetic field with 3 ms point durations and with 4 s between the presentations of each pattern. They were transmitted through the same telephone sensor coils employed in Experiments 3 and 4. The intensities within 2 cm, 4 cm, 6 cm, and 8 cm from either pickup coil when the field was generated from the CD was 1.4 microT, 0.5 microT (5 mG), 0.2 microT, and 90 nT, respectively. The primary intensity within the exposure volume was 80 nT.

Computer and Sound Card Specifications

The computer that generated the values producing the magnetic fields for use in experiments 1, 2, and 3 in the present studies was an IBM XT. This was the computer of choice because the increments of timing (i.e., 1 ms is truly 1 ms) were reliable. Due to the premise that experiments 4 and 5 required an audio output a computer with a 75 MHz processor and a TBS Montego Sound Blaster Pro Emulation sound card was used. It is also critical to remember that the magnetic patterns (not the sonic equivalents) were still generated in Experiments 4 and 5.

Statistical Analysis

In several experiments we have found no substantial differences between groups of rats for baseline latencies and the net differences (in sec) between Trial 2 and Trial 1 and between Trial 3 and Trial 1 have shown the most systematic and comparable values between and within experiments. Therefore, the net differences (not relative [i.e. (trial2 – trial1)/trial1]), thus using each rat as its own control, were used for all analysis. The dependent measures involved the net differences in sec in response latency between Trial 2 and the baseline and Trial 3 and the baseline.

Because the basic procedures were similar, all analyses involved at least a three-way analysis of variance with two (within subject) repeated measures (trials; days or week as in experiment 2) and one between level (treatment, i.e., sham field vs. magnetic field variations). Post hoc tests for main effects involved Tukey's set at $p < .05$. Post hoc tests for mixed interactions between within subject and between subject measures involved the appropriate combinations of paired *t*-tests and Tukey's, both set at $p < .05$. All analysis involved SPSS software on a Vax 4000 computer.

RESULTS

Experiment 1: Polarity Effects

The means and standard error of the means (SEM) for the differences in sec to respond to thermal stimuli relative to baseline measures after receiving a burst-firing magnetic pattern with either bipolar, positive, negative polarity components or sham field conditions are represented in Figure 1 for the first day of testing. Three-way analysis of

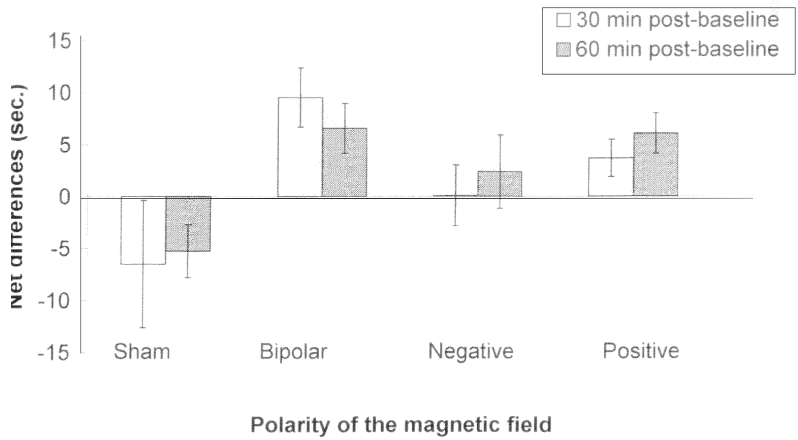

FIGURE 1. Means and SEM for the net time (s) to respond to the thermal stimuli for rats exposed to the burst-firing pattern with positive, negative, or bipolar characteristics on the first day of testing.

variance with two levels repeated (30+ and 60+ min for each of two days) and one level not repeated (properties of the magnetic field) showed there was a statistically significant main effect for the application of the magnetic field [$F(3,12) = 4.17$, $p < .05$, $eta^2 = 51\%$]. There was no statistically significant effects for the day of testing, trial of testing, or interaction between any of the repeated or between measures [all Fs < 1.50].

Post hoc analysis revealed that after 30 min of exposure to the field the rats exposed to the bipolar burst-firing pattern had significantly longer thermal latencies compared to sham exposed rats, while no other groups differed significantly from one another. However, 60 min after the beginning of the exposure (and 30 min after no exposure) rats exposed to either the bipolar and positive polarity treatments exhibited significantly more analgesia than the sham-exposed rats that did not differ from those exposed to the negative polarity field.

Experiment 2: Weekly Exposures

The means and SEM for the four weeks of testing when rats were exposed to the field conditions or to sham field conditions are shown in Figures 2 and 3. The most prominent effects from the three way analysis of variance were the main effect from the difference between the magnetic field and sham-field exposures [$F(1,14) = 58.27$, $p < .001$, $eta^2 = 80\%$] and the two way interaction between the magnetic field treatment and the week of testing [$F(3,42) = 4.59$, $p < .001$, $eta^2 = 25\%$]. There was also an interaction between the magnetic field treatment and when they were tested +30 min and 60+ min after the beginning of the treatment [$F(1,14) = 5.96$, $p < .05$, $eta^2 = 30\%$].

Post hoc analysis showed that the primary source of the interaction between treatments and weeks of treatment was due to the statistically significant increase in thermal latencies on the first, third, and fourth week of testing for the magnetic field exposed rats compared to sham exposed rats. However, there were no significant differences between magnetic field and sham-exposed rats during the second week of testing.

Post hoc analysis also demonstrated that the primary source of the interaction between treatments and trials was due to the significantly longer thermal latencies 60 min after exposure compared to 30 min after exposure for animals exposed to the burst-firing

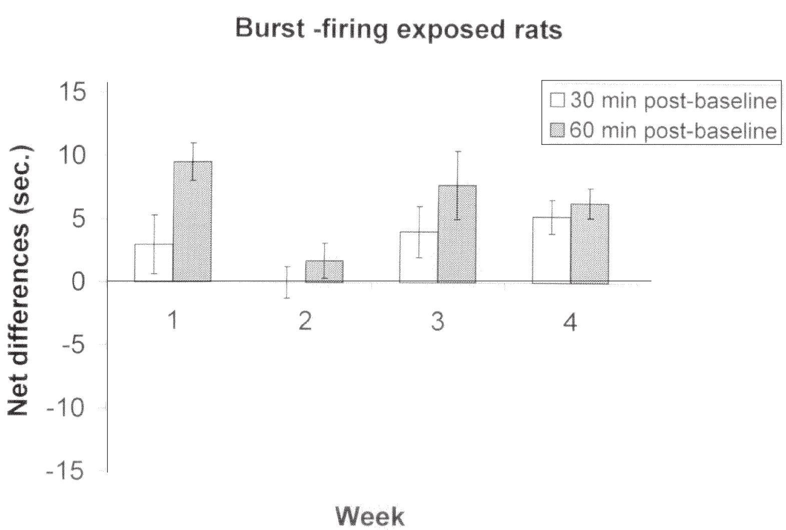

FIGURE 2. Means and SEM for the net thermal latencies (s) for rats exposed to the burst-firing magnetic pattern once a week for four weeks.

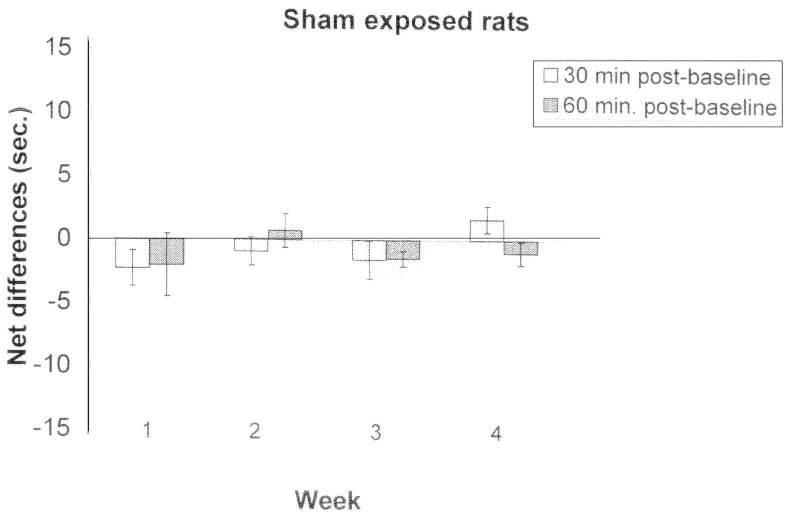

FIGURE 3. Means and SEM for the net thermal latencies (s) for rats exposed to sham field conditions once a week for four weeks.

magnetic pattern, while sham-exposed rats did not differ significantly over the two testing periods.

Experiment 3: Alternative Generation Coils

The means and SEM for the thermal latencies of rats exposed to the burst-firing field generated through the telephone pickup coils (rather than the iron core solenoids (or "nails") or to sham field conditions are displayed in Figure 4. Compared to the rats exposed to the sham-field conditions, the rats exposed to the burst-firing field generated through the telephone coils showed an increased analgesic response on the first day only [$F(1,20) = 4.63$, $p < .05$]. This was not evident (not shown) on the second day. The effect size for the analgesia on the first day of testing was about 18%.

Experiment 4: Generation by .wav Files

The means and SEM for the thermal responses after the rats were exposed to a burst-firing magnetic pattern generated as a .wav file or to the sham-field conditions are shown in Figure 5. The three-

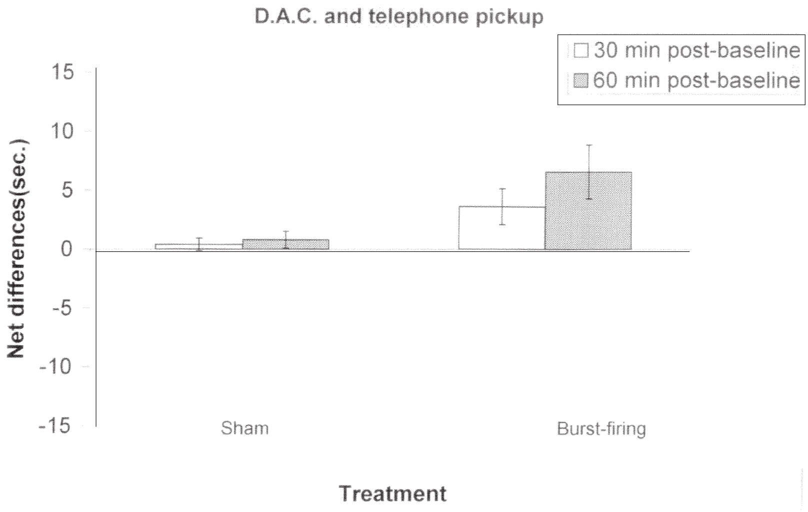

FIGURE 4. Means and SEM for the time (s) to respond to the thermal stimuli when rats were exposed to the burst-firing magnetic pattern or sham field conditions on the first day of testing when telephone induction coils were used to apply the magnetic field.

way analysis of variance with two levels repeated (days and trial) and one level not repeated (magnetic field treatment) revealed a significant main effect for the magnetic field treatment [$F(1,10) = 5.79$, $p < .05$, eta^2 = 37%]. The burst-firing exposed rats displayed stronger analgesia than the reference group. The application of the burst-firing magnetic pattern as a .wav audio file resulted in a significant increase in thermal responding compared to sham exposed rats. The main effect for the day of testing approached statistical significance [$F(1,10) = 3.75$, $p = .082$]. However, no other main effects (within or between measures) either approached or reached statistical significance [all F's <1.00].

Experiment 5: Generation from Compact Disc

Figure 6 shows the thermal latencies for rats exposed to the burst-firing magnetic field that was generated from a CD to telephone pickup coils or to the sham-field conditions. Three way analysis of variance with two levels repeated (two days of testing with two net trials per day) and one level not repeated (magnetic field treatment)

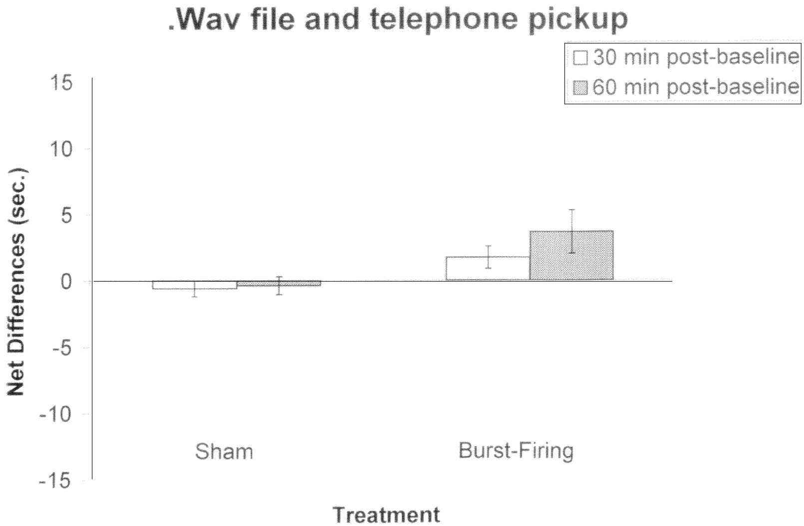

FIGURE 5. Means and SEM for the net thermal latencies (s) on the first day of testing when the magnetic pattern was transformed into a .wav file. A sound card was then used to produce the magnetic pattern, which was applied through telephone induction coils.

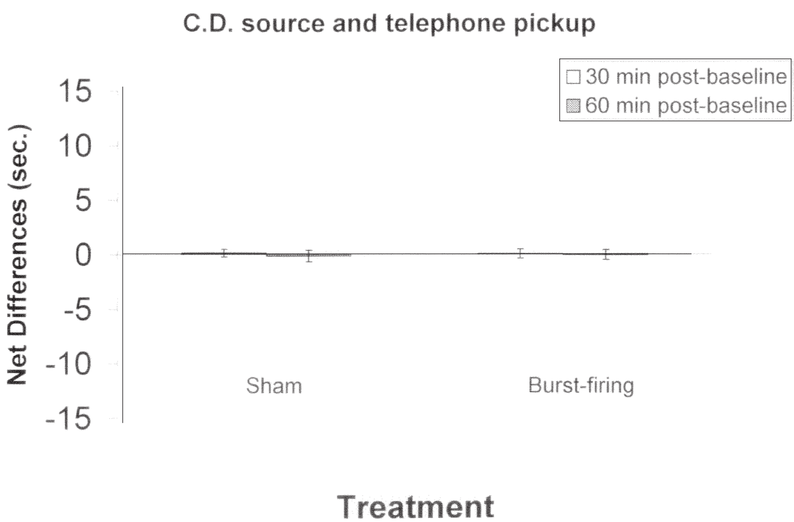

FIGURE 6. Means and SEM for the net thermal response times (s) when the magnetic pattern was transformed onto a CD source and generated using a sound card and applied through telephone induction coils.

discerned that there was no statistically significant difference between treatments [$F(1,12) = 0.12$, n.s.]. No other main effects or interactions between the repeated and between measures reached statistical significance [All F's < 1.00].

DISCUSSION

The results of the present study are congruent with those reported by Martin et al. (in press). They found a robust analgesia (similar to the effects of at least 4 mg/kg of morphine) to thermal stimuli in more than two hundred rats over several experiments when this same (burst-firing) pattern was presented once every 4 s for 30 min. The results of the current investigation also emphasized that the characteristics and the technique or method used to administer a magnetic field treatment is critical in eliciting different responses. For instance, the application of the burst-firing field as a positive polarity or as a bipolar signal gave rise to the strongest analgesia while the same burst-firing pattern restricted to the negative polarity did not significantly alter thermal thresholds.

A previous comparison between the positive and negative components of a static magnetic field did not appear to cause any clinically meaningful changes in heart rate or blood pressure among asymptomatic subjects (Hinman, 2002). With respect to transcranial direct current stimulations, it has been suggested that the effects are dependent upon polarity, duration and current strength of stimulation (Liebetanz et al., 2002). The studies suggest that the analgesic effects are dependent upon the, polarity and the software used to generate the magnetic pattern.

The polarization of individual cells has been proposed as a mechanism for field stimulation and defibrillation (Krassowska, 2003). Although the authors have used a complex magnetic field to generate the biological effects we propose that the positive component of the magnetic pattern is essential to generate the infraslow potentials (ISPO), which are a specific type of steady potential (SP). They are defined as oscillations of frequencies between 0.5 to 15 or more cycles per minute (Aladjalova, 1964), and appear to be related to the SP shift associated with learning and reward (Rowland, 1968).

Norton and Jewett (1965) reported that light anesthesia was accompanied by IPSO. The analgesia observed in our study might be considered comparable to a slight anesthesia. The ISPO also appears in an organism after a latent period of often 1 to 2 h after stress to the organism (Aladjalova, 1964). The maximum analgesia was attained 30 min after the cessation of magnetic field treatment and 60 min after the initial stressor (i.e., baseline measurement on the hotplate).

Oscillating and rotating magnetic fields have been shown to influence stress-induced analgesia (Kavaliers & Ossenkopp, 1987; Betancur et al., 1994; Del Seppia et al., 2000). The present authors' working hypothesis is that the complex magnetic pattern augments the ISPO associated with the stress response resulting in a slight anesthesia or analgesia. The ISPO cannot be responsible for this effect alone since the sham-referenced rats did not exhibit an analgesic response.

In experiment 2 the magnetic field treatment increased thermal latencies on the first, third, and fourth week of treatment, but not during the second week of testing. This may be due to a shifting of the mechanism associated with subsidence of the orienting response (Rowland, 1968). The initial analgesia (i.e., first week) could be due to the augmentation of the stress induced ISPO by the complex magnetic field treatment resulting in longer thermal latencies. However there is no analgesic effect during the second exposure (i.e., second day or week) due to the repetition of the stimulus (i.e., hotplate).

The authors suggest that the analgesia reappeared on the third and subsequent fourth week of exposures due to a shifting of mechanism allowing long-term structural alterations to occur. Scholz and Woolfe (2002) have stated that a central sensitization can occur leading to long-lasting changes in nociception thresholds and sustained for a period of time by transcriptional changes including induction of genes such as Cox-2 to generate PGE-2, which alters the excitability of neurons. The structural changes that may be occurring would involve a desensitization or inhibitory process, congruent with the induction of analgesia.

Here the authors hypothesize that the complex magnetic pattern may be influencing transcriptional changes resulting in the alteration of nociceptive thresholds after multiple exposures. Magnetic fields have been previously shown to influence the DNA binding behavior of transcriptional elements such as cyclic adenosine monophosphate binding element (cAMP) (Zhou et al., 2002) and c-fos (Hausmann et al., 2000; Hausmann et al., 2001). C-fos is a rapid indicator of neuronal activation and magnetic fields have been shown to alter the transcription of genes in cell lines including c-fos (Phillips, 1993). Fos has been proposed to be a third messenger to regulate the expression of specific target genes (Kovacs, 1998).

Previous work has demonstrated the coexistence of Fos protein and proopiomelanocortin (POMC) mRNA in the hypothalamic arcuate nucleus (Arc) after electroacupuncture treatment using techniques of in situ hybridization and immunocytochemistry (Zhang et al., 1996). These results suggest the activation of beta-endorphinergic (beta-EP) neurons in the Arc by electroacupuncture (EA) and implicate Fos in modulating POMC expression. These experimenters demonstrated that when c-fos expression is altered it is colocalized with an opioid precursor. Previous researchers have suggested that complex magnetic fields may influence the opioid system (Thomas et al., 1997).

The blockade of c-fos activation by magnetic stimulation has been shown to occur via sodium channels (Hausmann et al., 2001). It has been suggested that static magnetic fields with altering polarity gives rise to slow changes in the conformation of ion channels or enzymes, resulting in phosphorylation/dephosphorylation of sodium channels (McLean et al., 2001) which may be occurring 60 min following the beginning of the magnetic field treatment.

The analgesia was still present when the magnetic pattern was generated using the telephone pickup device (designed commercially to be an induction coil) and the digital-to-analogue converter or the telephone pickup device and a sound card when the magnetic pattern was converted into a .wav file. This would indicate that this effect is not mediated by the equipment used to generate this field but by the actual magnetic field itself. The mild discrepancies in the strength of the analgesia were more likely associated with the reduced intensity and volume of the field generated by the pickup coil. The field strengths were almost identical when the burst-firing pattern was generated by .wav or CD However, the latter source produced no evidence of analgesia.

The analgesia was not present when the magnetic pattern was transformed on to a CD format, or when applied in the negative polarity. The magnetic pattern exists as an electrical signal (i.e., is "alternating" in nature) when contained on the CD. In most audio devices, the signal is positive some of the time (50% on average) and negative some of the time. During the recording process, the polarity of the audio signal is typically inverted multiple times (Mark Levinson, 1996). When the magnetic pattern was converted onto the CD a number of 180° inversions of polarity could occur an odd number of times resulting in a net inversion of polarity. The authors are proposing that the magnetic pattern, when transformed on to the CD, exists in the negative polarity or some patterns were burnt in the negative and some in the positive polarity, resulting in a non-effective treatment.

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