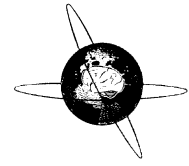




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Effect of low-frequency magnetic fields on brain electrical activity in human subjects

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Abstract

Objective: To measure the response rate of normal human subjects to a low-strength, low-frequency magnetic field (MF), using nonlinear quantitative analysis of the electroencephalogram (EEG).

Methods: Eight subjects were exposed to a series of trials, each consisting of the application of the MF (1 G, 60 Hz) for 2 s followed by a field-free period of 5 s, and the EEG was analyzed statistically using phase-space methods to assess whether the subject detected the MF.

Results: Each subject exhibited statistically significant changes in the EEG during presentation of the MF, as evidenced by increases in percent determinism and percent recurrence, two different measures of deterministic structure in the recorded signal, thereby indicating that the MF had been detected.

Conclusions: The 100% response rate manifested by the study group suggested that the ability to detect low-strength, low-frequency MFs is a common property of the human nervous system.

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Keywords: Nonlinear analysis; Recurrence plot; Magnetic field; EEG; Phase space

1. Introduction

A deeper understanding of the changes in brain electrical activity produced during application of magnetic fields (MFs) is the goal of different lines of research including transcranial stimulation (TS) (Terao and Ugawa, 2002), and evaluation of the public-health significance of fields in the environment (Portier and Wolfe, 1998). The major unresolved issues regarding TS relate primarily to therapeutic consequences, because the detection process is reasonably well understood. For environmental MFs, however, which typically are 3 or more orders of magnitude smaller than those used for TS, the central question concerns whether the fields are actually detected by human subjects. Effects of low-strength MFs on brain electrical activity were found in some studies; for example, subjects exposed to 3 Hz, 1 G, and to 50 mG, pulsed at 6–20 Hz exhibited significantly reduced spectral power, on average (Schienle et al., 1996;

Heusser et al., 1997). In another study, however, no average effect on spectral power was found after exposure to 100 mG, 60 Hz (Lyskov et al., 2001).

Mixed results also occurred when the effect of MFs on brain electrical activity was assessed within individual subjects. Exposure to 0.25–5.0 G, 35–40 Hz produced changes in the EEG in only 7 of 14 subjects (Bell et al., 1991). Application of 10–40 G DC altered the epileptiform spike activity in only 5 of 10 patients in the period immediately following application of the field (Dobson et al., 2000). Eleven subjects exposed to 0.8 G, 1.5–10 Hz exhibited increased spectral power, but 8 subjects exhibited no effect (Marino et al., 1996). These and other pertinent studies have been reviewed recently (Cook et al., 2002)

Various explanations could account for why MFs altered the EEG in some studies or subjects, but not others. The apparent inconsistencies could have arisen from inter-subject variations in sensitivity to the MF (Lyskov et al., 2001). The spectral properties of the MF may be important in determining its biological effect, with the result that field effects occur only within particular windows of frequency or

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field strength (Gartzke and Lange, 2002). Another possibility is that the absence of an effect in some subjects or some groups of subjects was due to a relative insensitivity of the methods used to analyze the EEG, which in all the previous studies were linear methods. Recent studies suggested that the EEG can exhibit nonlinear determinism (law-like behavior) due to low-dimensional chaotic sources (Krystal et al., 1996; Theiler and Rapp, 1996; Micheloyannis et al., 1998; Marino et al., 2002). An analytical approach that also took nonlinear effects into consideration might lead to a more consistent picture of the changes in brain electrical activity produced during application of MFs, possibly indicating that magnetodetection is a common human characteristic.

Our aim was to test the magnetodetection hypothesis by showing that detection of an arbitrary but environmentally relevant MF occurred in each subject in a representative test group. To accomplish this purpose, we compared the EEG within individual subjects obtained during the presence and the absence of the MF, using a novel method of analysis that was capable of capturing both linear and nonlinear effects that might be present (Marino, 2003).

2. Methods

2.1. Subjects

Eight clinically normal subjects were studied; their age in years and gender were 27/M, 34/F, 31/M, 18/F, 23/M, 45/F, 29/M, 28/F, for subjects 1–8, respectively. All procedures involving human subjects were reviewed and approved by the Institutional Review Board at our institution, including written informed consent. Scalp electrodes (Grass Instrument Co., Quincy, MA) were attached at C3, C4, P3, P4, O1, and O2 (International 10–20 system) and referred to linked ears; the ground was placed on the forehead. The electrode impedances (measured before and after recording the EEG (EZM5, Grass Instruments)) were always less than 3 k Ω . The signal was detected using an amplifier capable of resolving 0.1 μ V (Model 4400, Nihon Kohden, Irvine, CA), subjected to analog filtering to pass 0.5–35 Hz, digitized at 512 Hz (12 bit), and stored on a computer hard-drive. Frequencies above 35 Hz were at least 40 db below the strongest frequency in the 0.3–35 Hz range.

2.2. Exposure system

Magnetic fields were produced using a pair of coaxial coils, each 130 cm in diameter and consisting of 250 turns of copper wire; the coils were separated by 65 cm (the Helmholtz condition) by means of a wooden frame (Bell and Marino, 1989). The coil current was obtained from a function generator (Model 182A, Wavetek, San Diego, CA) and amplifier (Model 7500, Krohn-Hite, Avon, MA), and controlled by a computer-generated timing signal (Fig. 1).

The subjects sat on a comfortable plastic chair in a dark room with their eyes closed; their sagittal plane was perpendicular to the MF produced by the coils. A magnetic field of 1 G, 60 Hz was used; it was uniform to within 5% in the region of the head and upper chest (within 20% over the thorax and pelvis), as measured using a magnetometer (Bartington, MAG-03, GMW, Redwood City, CA). The field strength and frequency were chosen because they can be found in both the general and workplace environments, and are comparable to fields studied previously (Bell et al., 1991; Marino et al., 1996, 2002). The MF was a subliminal stimulus; its presentation was not accompanied by any visual or auditory cues to the subjects, and consequently the subjects were unaware of the precise times when it was applied. The equipment that controlled the coils and recorded the EEG was located in a room adjacent to that occupied by the subject. The average 60 Hz background magnetic field at the location of the subject was 0.1 mG. The average geomagnetic field at the location of the subject was 432 mG, 68.4° below the horizontal. The geomagnetic component along the direction of the 60-Hz field was 156 mG.

2.3. Procedure

We chose an intra-subject design because of its greater sensitivity, compared with an inter-subject design. The subject underwent a series of trials, each of which consisted of the application of the field for 2 s (*E* epoch), followed by a stimulus-free period of 5 s. The EEG signal was measured throughout each trial; the portion of the signal from the last 2 s of each trial was used as the control (*C* epoch) for the corresponding *E* epoch, and the existence of an effect due to the MF was determined by comparing *E* versus *C*. In addition, as a control procedure, the signal from the 2 s preceding the *C* epoch was defined as the sham (*S* epoch) and was analyzed (*S* versus *C*) to evaluate the possibility of false positive results attributable to our analytical method. A minimum of 60 trials were run (Fig. 1).

As a positive control procedure, a second set of identical trials was carried out during the same experimental session using light as the stimulus (2 s on, 5 s off during each trial). The light source was mounted at eye level and produced less than 50 lumens at the corneal surface of the eye; it could be seen by the subjects even though their eyes were closed. The rise-times of the current through the coils and the light source were approximately 1 μ s.

2.4. EEG analysis

Trials that contained any movement artifacts as assessed by visual inspection of the graphical record were removed from the recorded signal. The remaining time series, which consisted of voltages at discrete times, was embedded in phase space; the method of phase-space embedding is discussed elsewhere (Jeong et al., 2001). An embedding dimension of 5 and a time delay of 1 were chosen during

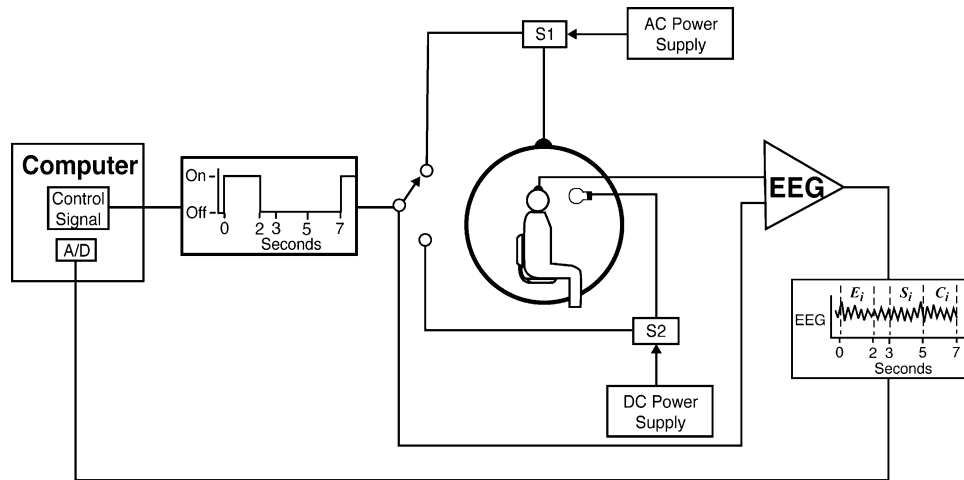


Fig. 1. Schematic representation of the experimental system. A computer-generated timing signal controlled switches for the magnetic field and the light (S1 and S2, respectively). The timing signal was also fed into one of the channels of the EEG amplifier to facilitate identification of the exposed (*E*), sham (*S*), and control (*C*) epochs of the EEG in each trial (the *i*th trial is illustrated). Circle, field-producing coils.

preliminary analysis of the data on the basis that they resulted in the most sensitive characterizations of the EEG epochs. The result of the embedding procedure was a geometrical representation of the evolution of the system's state vector.

To quantitate the phase-space appearance of the state vector, we produced 2-dimensional plots consisting of points that each corresponded to a pair of state vectors that were 'near' one another ('recurrence plot') (Eckmann et al., 1987); two states were defined as near only if both were contained within a 5-dimensional sphere having a radius less than 15% of the minimum radius such that all points were near. Recurrence plots can reveal patterns in the time series that cannot be detected by eye (Eckmann et al., 1987; Webber and Zbilut, 1994).

The recurrence plot was quantified using percent recurrence (%R) (which is the correlation sum evaluated at the chosen scale (15%)) and percent determinism (%D). %R was defined as the number of recurrent points divided by the possible number of recurrent points. %D was defined as the number of recurrent points (above a preset minimum number) located on lines parallel to the main diagonal of the plot, divided by the number of recurrent points; more detailed explanations are given by the investigators who developed the quantifiers (Webber, 1991; Zbilut and Webber, 1992; Webber and Zbilut, 1994). %R is a measure of the extent to which the signal is correlated with itself in phase space. %D characterizes the tendency of the system to re-visit the same area of the attractor, and is therefore a measure of the amount of rule-obeying structure in the signal. Both recurrence-plot parameters are based on the characteristics of the differential equations that govern the dynamical activity of the system, rather than on changes in known specific physiological processes; consequently the parameters cannot presently be identified with known cellular or molecular processes.

Calculation of %R and %D was carried out using software provided by Webber (Webber, 2003) and independently verified using a custom code (Matlab, Mathworks, Natick, MA).

2.5. Statistics

In preliminary studies we observed that the effect of the stimuli did not occur uniformly throughout the 2 s intervals in which they were presented. To maximize the likelihood of detecting a difference between corresponding *E* and *C* epochs, we followed a systematic procedure aimed at isolating the epoch segments most affected by the stimulus. Using the EEG from subject no. 1, corresponding epoch segments ('windows') were used to compare *E* versus *C*, and *S* versus *C*. Essentially all possible window parameters were considered, and those that yielded the lowest probability (*P*) for the comparison (using the *t* test) of *E* versus *C* when *P* > 0.05 for *S* versus *C* were then applied prospectively to evaluate the effect of the stimuli on %R and %D in the remaining 7 subjects. In instances where 6 statistical tests were performed on the subject (calculation of %R for each of 6 electrodes), the criterion for accepting the conclusion that an event-related change in scalp potential actually occurred was that the MF resulted in at least two significant differences (*P* < 0.05). It can be shown using the binomial theorem that this condition was sufficient to eliminate (*P* < 0.05, overall) the possibility of a family-wise error regarding rejection of the null hypothesis.

In each statistical test, the first 5 trials were discarded and the next 50 artifact-free trials were used to compare the values of the nonlinear quantifiers, using the *t* test. The data are presented in terms of the mean ± SD of %R and %D; the tests involving the two quantifiers were regarded as independent planned comparisons.

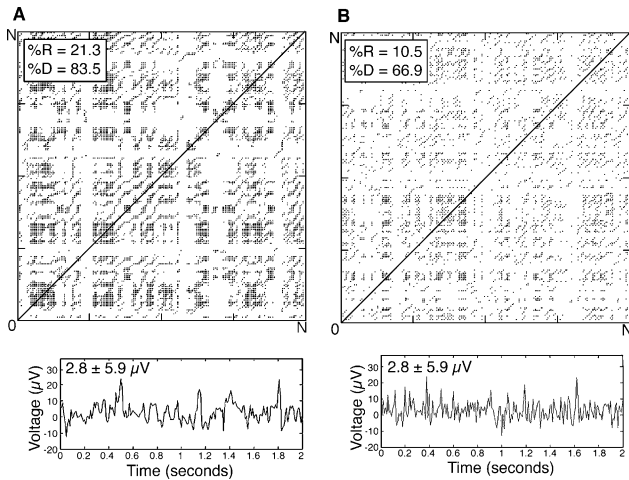


Fig. 2. Recurrence plots produced from 2 s of EEG data derived from an occipital electrode. The plots are symmetrical about the diagonals, which were added. (A) Original EEG (bottom) and associated plot (top). (B) Signal formed by randomizing the EEG (bottom); the recurrence plot (top) of the randomized signal is less deterministic than the plot for the original EEG (A, top). Recurrent points form distinct patterns characterized by %R and %D which, unlike the mean and standard deviation, are sensitive to nonlinear determinism present in the signal. *N*, number of recurrent points.

3. Results

Recurrence plots constructed from the EEG (Fig. 2) were similar to the complex two-dimensional patterns typical of physiological time series (Webber, 2003) and chaotic deterministic systems (Eckmann et al., 1987). The essential feature of the plots was that their texture resulted directly

from the dynamical electrical activity of the brain; when the dynamical correlations in the EEG were reduced by randomizing the signal (Fig. 2B), the mean and standard deviation of the resulting signal were unchanged but %R and %D decreased, indicating that the parameters characterized the determinism in the EEG more completely than did the mean and standard deviation.

The MF was detected by each subject as evidenced by the occurrence of statistically significant changes in %R calculated from at least two electrodes in each subject (Fig. 3). First, the EEG from subject no. 1 measured during the magnetic-field trials was unfolded in phase space, and %R was calculated for corresponding portions of the *E* and *C* epochs in each trial. We found that a 190 ms window centered at 215 ms after commencing application of the field yielded the lowest significant *P* value for *E* versus *C* (window centered at 5.215 s, width of 190 ms) when *P* was not significant for *S* (3.215 s, width of 190 ms) versus *C*.

When the 190 ms window was shifted to earlier or later times by more than 30 ms, the *E* versus *C* comparison was not significant, indicating that the subject's response started at about 100 ms. A similar delayed response has also been reported in rabbits (Marino et al., 2002).

The window width and location thus determined were then applied prospectively to 7 additional subjects, in 7 independent experiments, to ascertain the effect of exposure to the MF, and statistically significant differences in %R were found in each experiment (Fig. 3).

Significant differences were also found in %D for each subject, particularly at the occipital electrodes (Fig. 4),

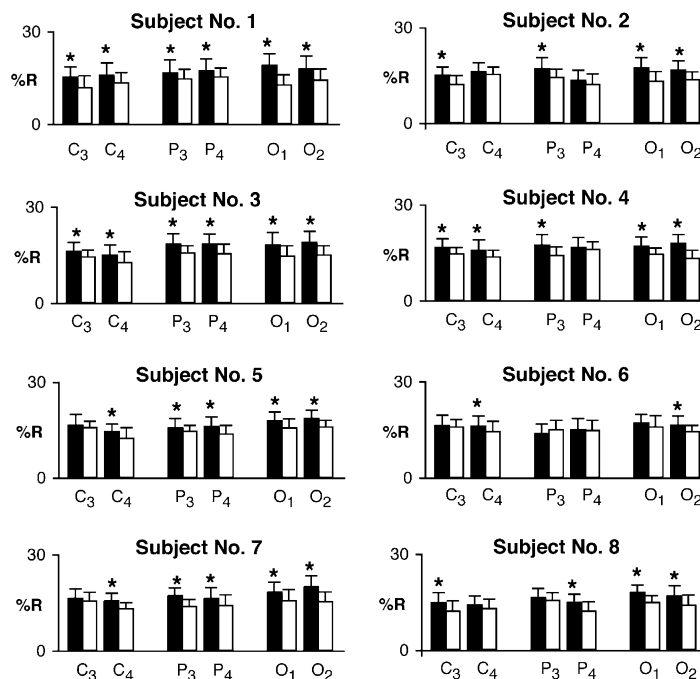


Fig. 3. Effect of magnetic-field exposure on the EEG derived from central, parietal, and occipital electrodes, assessed using %R. The window (width of 190 ms) for comparison of the exposed and control epochs was centered at 215 ms from the beginning of the epoch. (■) Magnetic field; (□) control. Mean \pm SD. **P* < 0.05.

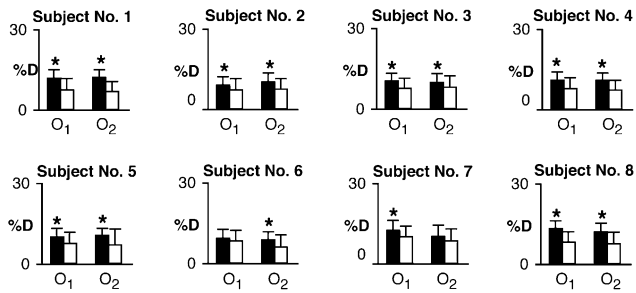


Fig. 4. Effect of magnetic-field exposure on the EEG derived from occipital electrodes, assessed using %D. The window (width of 190 ms) for comparison of the exposed and control epochs was centered at 215 ms from the beginning of the epoch. (■) Magnetic field; (□) control. Mean \pm SD. * $P < 0.05$.

again indicating that the MF was detected by each subject. There were no false positive differences (S versus C) from any electrode for either %R or %D (not shown). Also, during sham experiments in which the coils were not energized during the E epochs, there were no significant differences in sham E versus C (not shown).

Light was also detected by the subjects, as evidenced by the large increases in %R and %D that occurred at each occipital electrode during the presentation of the stimulus (Fig. 5). As previously, the optimal window parameters were determined using subject no. 1 (190 and 175 ms for width and center-location, respectively) and were used prospectively for the remaining subjects, all of which reacted strongly to presentation of the light. Representative results from two subjects are shown in Fig. 5; there were no cases of a false positive result (not shown).

4. Discussion

We assumed that a method of analyzing the EEG that did not parse its activity into linear and nonlinear parts but rather characterized the determinism actually present in the signal would facilitate detection of the effects of MFs.

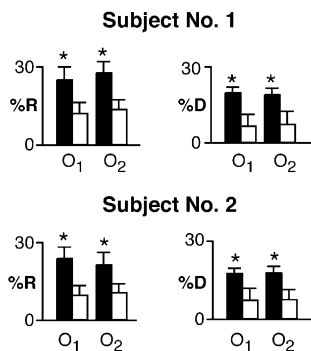


Fig. 5. Effect of a light stimulus on the EEG derived from occipital electrodes, assessed using %R and %D. The window (width of 190 ms) for comparison of the light and control epochs was centered at 175 ms from the beginning of the epoch. (■) Light; (□) control. Mean \pm SD. * $P < 0.05$.

Based on that assumption, we used a novel analytical method (Marino, 2003) to compare the EEG within individual subjects in the presence and absence of the field. In each subject, %R and %D calculated from the occipital EEG at 120–310 ms from the onset of field presentation were altered, compared with the respective controls (Figs. 3 and 4). No false positive comparisons were found when the same mathematical procedures were used to compare sham-exposed and control segments, indicating that neither our analytical method nor nonstationarity in the EEG could explain the results.

Several lines of evidence indicated that the field-induced alterations in the EEG reflected a true physiological response, and not solely a physical effect due to the interaction of the field with the electrodes. First, any physical effect would have been expected to begin at $t = 0$, because the rise-time of the current that produced the magnetic fields was nil. However, the observed response commenced 120 ms after the beginning of the E epoch; such a delay could be explained by a detection process in the nervous system that included an afferent signal, some processing of the information in the brain, and electrotonic propagation of that brain activity to the scalp electrodes. Second, the EEG changes induced by both the field and the light occurred only after a similar delay (Figs. 3–5). Because of the great difference in frequency between the two stimuli, the occurrence of a similar delay was better explained by assuming that both changes were physiological, rather than by assuming that two electromagnetic fields which differed greatly in frequency had produced the same kind of physical effect. Third, field-induced EEG changes identical to those described here were observed in rabbits, but the effect disappeared when the measurements were made after the animals had been killed (Marino et al., 2002), suggesting that a passive interaction with the field could not explain the statistical differences we found here between the EEG measured in the presence and absence of the field.

It could be argued that the effects of MF exposure might persist beyond the 2 s exposure epoch, and that therefore the choice of the control was inappropriate. However, the E and C epochs differed significantly (Figs. 3 and 4), indicating that any persistent effect due to MF exposure did not prevent us from establishing the occurrence of an effect due to the field. Moreover, all comparisons of S versus C were statistically insignificant, implying that the EEG returned to its pre-exposure baseline within 3 s after termination of MF exposure. This implication is consistent with our previous observation that the response to a 10 Hz MF returned to baseline within about 1 s (Bell et al., 1994). Finally, the published reports that have documented persistence of MF effects on the human EEG all involved exposure conditions (field strength, frequency, duration of exposure) that were far different than those used in the present study (Cook et al., 1992; Lyskov et al., 1993; Vorobyov et al., 1998; Crasson et al., 1999). Based on these considerations, and those above, we conclude that the 1 G,

60 Hz field was transduced by each of the subjects, resulting in a change in brain electrical activity.

Other investigators have described effects of electromagnetic fields on brain electrical activity (Bell et al., 1991; Marino et al., 1996; Schienle et al., 1996; Heusser et al., 1997; Dobson et al., 2000; Lyskov et al., 2001). The novel aspect of our results is the consistency with which we detected a deterministic response to the field in the EEG. Neglecting subject no. 1, whose EEG was used to construct a discriminant procedure for detecting field-induced effects, an effect of the field was found in occipital electrodes from all 7 subsequent subjects, using two different parameters (Figs. 3 and 4). There are no previous reports of a similar consistent effect of an environmental-strength electromagnetic field on brain activity.

In preliminary studies, we were unable to consistently detect an effect of the field on the EEG when we assumed that the response was present throughout the 2 s exposure epoch. We were therefore led to evaluate windowed segments of the EEG. It was previously shown that a 1 ms TS pulse could alter nonstationary processes in the brain (percept formation occurring in the period immediately after presentation of the visual stimulus) (Kamitani and Shimojo, 1999). Our results indicate that the response to a MF could itself be nonstationary in the sense that the induced change in brain activity varied during application of the field.

The mechanism by which low-strength magnetic fields can alter brain activity is unknown but, unlike TS (Terao and Ugawa, 2002), the mechanism probably does not involve direct alteration of the kinetics of voltage-sensitive ion channels in the neuronal membrane (Sonnier et al., 2000, 2003). Among the other issues not yet addressed are those involving field and individual thresholds, the role of the spectral properties of the field, and the possibility that neurological or other abnormalities may affect the results. For example, in a group of 10 rabbits, only the animal that had an abnormal EEG was unaffected by exposure to a high-frequency low-strength field under the conditions studied (Marino et al., 2003).

In summary, the results suggested that the ability to respond to the presence of 1 G, 60 Hz is a common characteristic of human subjects. The increased sensitivity for detecting the effect of MFs, compared with the previous studies (Marino et al., 1996; Heusser et al., 1997; Portier and Wolfe, 1998), can be explained by assuming that dynamically nonlinear neuronal systems facilitated detection of the field.

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