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Simulated MR Magnetic Field Induces Steady-State Changes in Brain Dynamics: Implications for Interpretation of Functional MR Studies

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We examined whether a magnetic field comparable to one of the fields produced during MRI induced steady-state changes in brain electrical activity while the field was applied (called a presence effect to distinguish it from evoked potentials). The electroencephalogram was measured from standard scalp locations in the presence and absence of 100-200 μT, 60 Hz, and the effect of the field was evaluated by nonlinear (recurrence analysis) and linear techniques; individual subjects served as their own controls. Using recurrence analysis, changes in brain activity lasting 1 sec (the longest interval considered) were found in 21 of 22 subjects ($P < 0.05$ for each subject). The presence effect was not detected using linear analysis and was reversible, as indicated by a return of brain activity to baseline levels in all subjects within 2 sec of field offset. The possible role of artifacts or systematic errors was ruled out by studies using electrical phantoms and by analyses of electroencephalograms recorded during sham exposure. It is reasonable to expect that actual scanner magnetic fields also produce nonlinear steady-state perturbations of brain dynamical activity. The effect may influence the picture of brain connectivity inferred in some functional MR studies. Magn Reson Med 64:349–357, 2010. © 2010 Wiley-Liss, Inc.

Key words: nonlinear analysis; brain electrical activity; limitation on fMRI; electric fields; magnetic fields

Cognitive activity is mediated by temporal-spatial interactions involving specialized regions of the brain (1). The interactions are commonly studied using functional MRI (fMRI) employing blood-oxygen-level-dependent (BOLD) contrast imaging (2).

Averaged images obtained when subjects were and were not performing particular tasks are typically used to identify brain regions that mediated task-related cognitive processing (3,4). This strategy is based on some problematical assumptions and has neuropsychological drawbacks (5), but it affords good statistical power for detecting BOLD signals (6).

In MRI, static (0 Hz) magnetic fields of 1-9 T align nuclear spins, high-frequency magnetic fields (10–400 MHz) of about 0.2 μT induce transitions between spin states, and low-frequency magnetic fields (100-1000 Hz) of about 50 μT produce imaging gradients (7); in fMRI, gradient parameters produce additional magnetic fields. Physical law and physiologic conditions in the brain (blood flow, tissue motion, cell movement, motion of the head) result in the simultaneous presence of electric fields (8).

Human subjects can detect magnetic fields, as evidenced by their ability to trigger onset and offset evoked potentials (9). We were interested in whether, in addition to these transient changes in brain electrical activity, magnetic fields relevant to those used in MRI also produced continuous changes during the time the field was applied ("presence effect"). Depending on the dynamical nature of the effect (see below), such a finding would enhance the possibility that BOLD data obtained during functional imaging could be influenced by a direct effect of scanner magnetic fields on brain activity, thereby confounding BOLD changes triggered by the cognitive stimuli.

We recently described a method for determining whether a sensory stimulus produced a presence effect, as evidenced by steady-state changes in brain electrical activity (10). Using this method, we tested the hypothesis that a magnetic field comparable to a field generated during an MR scan produced changes in human brain electrical activity that persisted until the field was removed.

MATERIALS AND METHODS

Subjects

Twenty-two clinically normal subjects were studied: nine males (age range 20–51 years) and 13 females (18–63 years). The subjects were informed of the goals, methods, and general design of the investigation but were not told exactly when the magnetic field would be applied during the experimental session. Written informed consent was obtained from each subject prior to participation in the study. The Institutional Review Board at the LSU Health Sciences Center approved all experimental procedures.

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Stimuli

We applied uniform (±5% throughout the head region) magnetic fields of 100–200 μT, 60 Hz, for 2 sec (onset and offset <10 ms), with an interstimulus interval of 5 sec (trial of 7 sec). The time-dependent magnetic fields used in scanners include Lamour-frequency sinusoids convolved with a sinc function and gradient fields (typically square or trapezoidal pulses) whose repetition rates approach 60 Hz. For several reasons, we did not attempt to mimic the magnetic environment of a typical echo-planar image (EPI) acquisition. First, our goal was to produce evidence that the presence of a magnetic field associated with any reasonable acquisition conditions had the potential to affect brain activity. To accomplish this goal, it was enough that the field used in the study was present in the Fourier sense (see Discussion) in a typical fMRI study. Second, critical conditions for testing our hypothesis included avoidance of potential confounding stimuli, for example, onset and offset evoked potentials due to magnetic and acoustic stimuli, and the persistence of a field for a duration long enough to permit experimental determination of a steady-state effect. The short readout time and transient fields used in EPI did not satisfy the necessary conditions and would therefore have complicated interpretation of the results. Third, to achieve exposure conditions that were readily reproducible and suitable for theoretical analysis of possible biophysical interaction mechanisms, it was desirable that the field be uniform throughout the subject's brain. This condition would not have been attained had the temporally and spatially complex fields used in EPI been employed. We assumed that a brain response to the fields used in this study would support an inference that actual MRI fields would yield similar results if the technical difficulties of performing the experiment in a scanner were overcome.

Seventeen subjects were exposed to 200 μT; an additional five subjects were exposed to 100 μT to evaluate the possibility that effects were proportional to field strength. Differences related to field strength were not observed; consequently, the data from the two subject groups were combined for analysis. The magnetic field was applied in the subject's coronal plane using a paired set of coils (Fig. 1a); construction details are given elsewhere (11). The subjects were exposed (eyes closed) in an isolation chamber to reduce the presence of random ambient stimuli. All electrical equipment was located outside the chamber; the absence of both uncontrolled sensory cues and direct perception of the field was verified by interviewing the subjects at the end of the experimental session. Magnetic-field measurements were performed using a triaxial magnetometer (Bartington, MAG-03; GMW, Redwood City, CA).

As a positive control, a binaural 424-Hz tone (frequency chosen arbitrarily) was presented for 2 sec (onset and offset <10 ms), with an interstimulus period of 5 sec; the sound pressure at the location of the subject was 65 dB.

Electroencephalogram Measurements

Electroencephalograms (EEGs) were recorded from O_1, O_2, C_3, C_4, P_3, and P_4 (International 10–20 system) referenced to linked ears, using gold-plated electrodes attached to the scalp with conductive paste; electrode impedances were less than 10 kΩ. The signals were amplified (Nihon Kohden, Irvine, CA), analog-filtered to pass 0.5–35 Hz, sampled at 300 Hz using a 12-bit analog-to-digital converter (National Instruments, Austin, TX), and analyzed offline.

Each EEG signal, V(t), was divided into consecutive 7-sec intervals (trials), with stimulus onset at $t = 0$, offset at $t = 2$ sec, and an interstimulus period at $2 < t \leq 7$ sec. Trials containing movement or other artifacts as

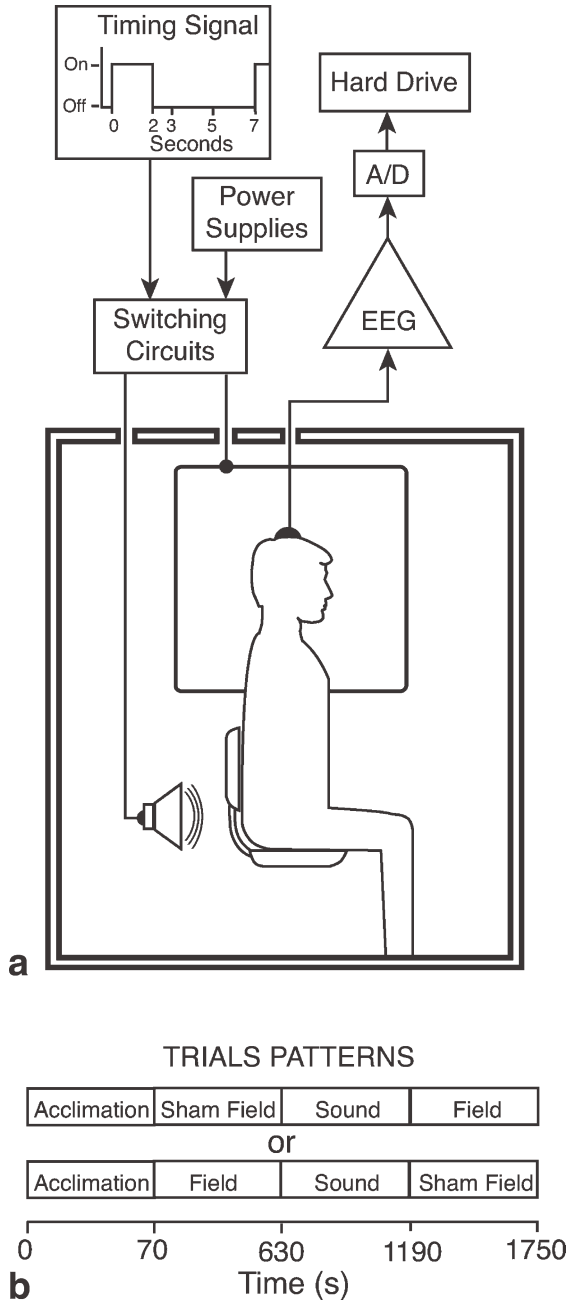

FIG. 1. Detection of stimulus-induced changes in the EEG. **a:** Schematic diagram of equipment used to apply stimuli and measure the EEG. A timing signal controlled application of the magnetic-field and auditory stimuli (on for 2 sec, off for 5 sec). **b:** Organization of trials in the experimental sessions.

assessed by visual inspection (12) were discarded (<5% of the trials), and the artifact-free trials were digitally filtered between 0.5 and 35 Hz.

In general, as a consequence of Faraday's law, EEGs measured while a subject is exposed to magnetic fields contain (1) voltage spikes that occur when the field strength changes abruptly; and (2) a periodic induced voltage at the frequency of the applied field (13). Measurements on electrical phantoms of the human head exactly reproduced the spikes seen in the EEGs. In both instances, the spikes lasted less than 30 ms (9) and therefore were not present in the epochs we analyzed (see below). The 60-Hz signal was removed by analog and digital filtering, as described above. The experiments with phantoms also established that motion of the phantom of less than 1mm (the maximum amount that could have occurred and not been detected as a movement artifact in the EEG) did not produce a detectable response. Ion motion in the phantom (rate comparable to blood flow) also produced no detectable response. The reliability of these results was verified by mathematical modeling using the characteristics of the magnetic fields we employed and assuming a reasonable model for the human head.

Because of the relative simplicity of the magnetic environment we employed, we did not experience the severe difficulties normally associated with attempts to make EEG measurements in MR scanners (13).

Following an acclimation period, every subject underwent three blocks of trials (80 trials/block); the magnetic field was applied in either the first or third block, as determined randomly from subject to subject (Fig. 1b). The data from the block where the field was not applied were analyzed as a negative control (sham field). The auditory stimulus was applied in the middle block (positive control). All results were based on data from at least 50 trials.

Nonlinear Analysis

We used "nonlinear" in the dynamical sense; we meant that cognitive processing was assumed to be governed by differential equations that had the mathematical property of nonlinearity. We termed methods designed to analyze such systems as nonlinear methods. The occurrence of dynamic nonlinearity in the electrical signals measured from the scalp during cognitive processing has long been recognized (6,14–18).

We recently described a nonlinear method for detecting a stimulus-induced presence effect in the EEG (10). Briefly, V(t) was embedded in a five-dimensional phase space using a time delay of 5 points (17 ms) (19). The embedding conditions were chosen empirically because there are no theory-driven procedures applicable to the EEG (20). The resulting trajectory was mapped to a two-dimensional recurrence plot by placing a point at (i,j) whenever the *i*th and *j*th state vectors in the trajectory were near (defined as within 15% of the maximum [Euclidean] distance between any two states) (21). Recurrence plots reveal dynamic patterns that cannot be detected by eye or by conventional linear techniques.

Recurrence plots can be quantified in many different ways (22); we used the variable *percentage determinism* (%D), defined as the number of points in the plot that formed diagonal lines, because initial studies showed that %D was particularly efficient for detecting steady-state changes in the EEG induced by magnetic fields (10). Unlike variables used to characterize nonlinear mathematical systems, fractal dimension and Lyapunov exponents as examples, calculation of %D did not require that the time series be stationary (a condition that is not satisfied by the EEG). From a formal viewpoint, %D is a measure of the tendency of the system to revisit the same area of its attractor in phase space and is therefore a measure of the amount of rule-obeying structure in the signal. The advantage of %D is that it can quantitate the recurrence plot; the disadvantage is that it does not provide direct insight into the physiologic basis of the dynamical activity. Computation of %D required specification of the minimum number of consecutive diagonal points taken to count as a line; we chose two points. All calculations were performed using publicly available software (http://homepages.luc.edu/~cwebber) and verified using a custom MatLab code (MathWorks, Natick, MA).

Brain potentials were evoked 100–500 ms after onset and/or offset of magnetic fields, even though the field is not consciously perceived (9,23,24). To achieve our present goal of detecting continuous change in brain activity that occurred *during* application of the field, we analyzed the evoked-potential-free interval in V(t) at $0.5 < t \leq 1.5$ sec (300 points), which we regarded as the field-exposed epoch (E); the results did not depend on the location of the interval chosen for study (0.5–2 sec, possible range) or on its length (0.33–1 sec range considered). The control epoch (C) was $5.5 < t \leq 6.5$ sec (identical results were obtained when $4.5 < t \leq 5.5$ sec was used as the C epoch). In addition, to facilitate evaluation of the reversibility of the presence effect, we defined the reversibility-control epoch (R) at $3.5 < t \leq 4.5$ sec. The relative location of the E, R, and C epochs in a typical trial is shown in Fig. 2a.

Experimental Design and Statistics

For each electrode derivation in each block of trials, the values of %D computed from the E and C epochs in V(t) (Fig. 2a) were compared using the paired *t* test at a pairwise significance level of $P < 0.05$ (identical results were found using the Wilcoxon signed rank test). The probability of observing ≥ 2 significant differences by chance at $P < 0.05$ in six tests (six electrodes) is 0.024. Consequently, if ≥ 2 tests were pairwise significant, we concluded that the presence of the field had altered the subject's brain electrical activity (presence effect). We analyzed the sham-exposure data to determine the frequency of a false-positive effect.

Whenever we found a significant difference between the E and C epochs, we examined whether there was also a significant difference between the R and C epochs (Fig. 2a). If none was found, we concluded that the presence effect was reversible in the sense that brain electrical activity had returned to baseline within less than 2 sec after field offset.

We also assessed whether the presence effect was a steady-state effect. The term *steady state* is used here to mean a change in the EEG that occurred following presentation of a magnetic field and that continued until

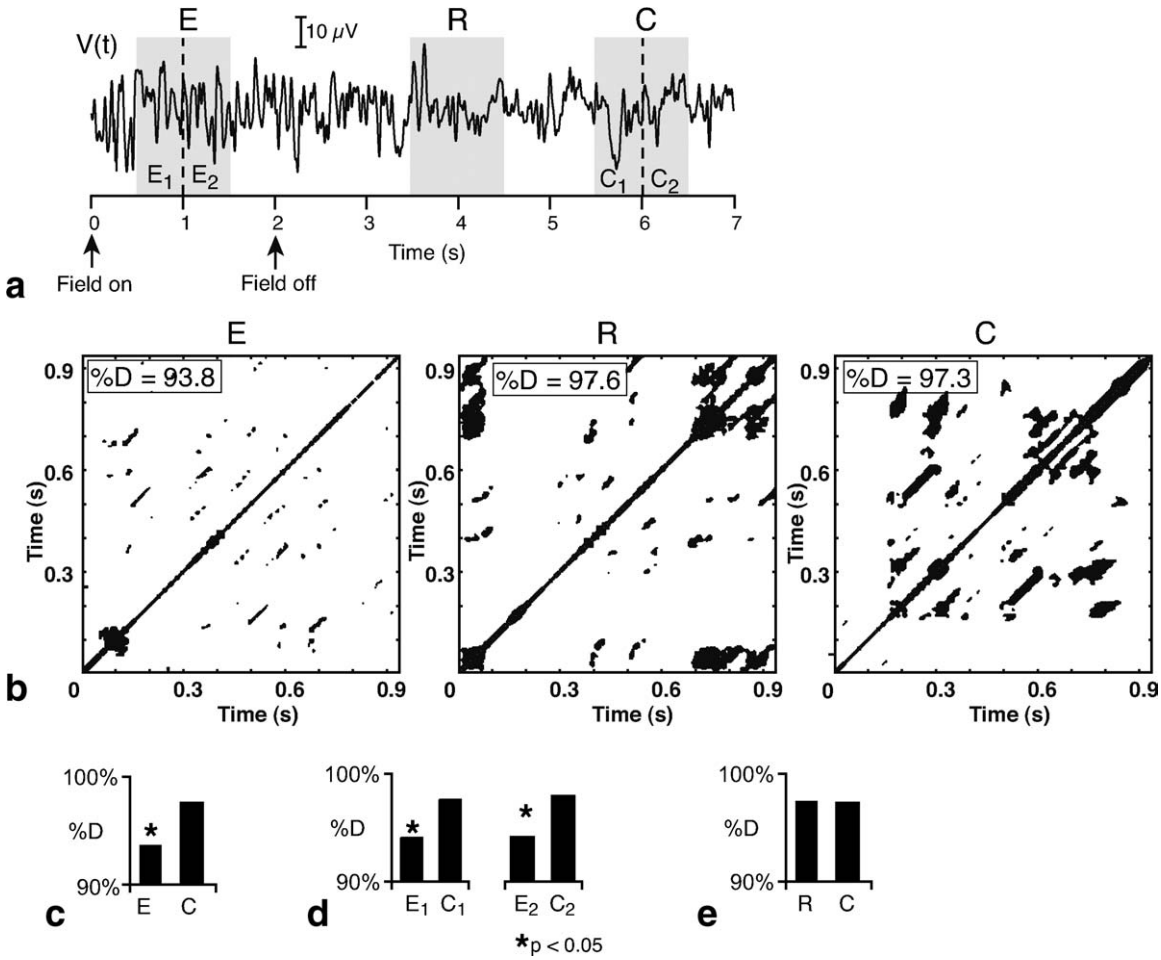

FIG. 2. Recurrence analysis to detect a magnetic-field-induced presence effect in the EEG at O_1 from subject S1. **a:** A randomly selected trial (the spike artifacts at t = 0–0.03 and t = 2.0–2.03 sec were removed for clarity) showing the locations of the epochs used to study the presence effect. The E and C epochs were compared to detect the presence effect. The R and C epochs were compared to establish its reversibility. The subepoch segments (E_1, E_2, C_1, C_2) were compared to assess whether the presence effect was steady state (continuous throughout E). **b:** Recurrence plots for each of the indicated epochs in the trial (at the scale shown, the individual points in the plots are not resolved). **c-e:** Results of the comparisons (73 trials). The standard errors are not resolved at the scale shown.

the field was removed. Whenever we found a significant difference between the E and C epochs, the E epoch was subdivided into two 150-point segments (500-ms bins), and each was compared with the corresponding segment in the C epoch (Fig. 2a). We regarded an effect as steady state if both E segments differed ($P < 0.05$) from the corresponding C segments in at least two electrodes.

To determine whether the presence effect could be detected by linear analysis of the EEG, all of the comparisons described above were repeated using V(t) directly (no phase-space embedding). In each trial, V(t) was averaged over the E epoch

$$\left(V_{RMS} = \left[\sum_{i=1}^{300} V_i^2 / 300 \right]^{\frac{1}{2}} \right) \quad [1]$$

and the resulting values were compared with the corresponding values from the C epochs to test for the presence of linear steady-state effects. We employed time averaging because it is a time-domain-based method, like recurrence analysis; other forms of linear analysis (spectral analysis using either absolute or relative EEG power) gave the same results as time averaging. If a change in brain activity was detected in %D but not in V(t), we concluded that the change was nonlinearly related to the stimulus.

The sound trials were analyzed using the same nonlinear and linear methods used to analyze the field trials.

Modeling

To examine the ability of recurrence-plot analysis to detect deterministic activity, we used a model mathematical system constructed to have specific deterministic (law-governed) properties. Nonlinear determinism in the EEG was mimicked by adding 300-ms segments of random-phase 10-Hz sine waves to 50 2-sec intervals of baseline EEG; the root mean square values of the signals (added at t = 0.85–1.15 sec) were equal to those of the corresponding baseline trials (Fig. 4b, left column). The augmented EEG was analyzed using both recurrence plots and time averaging to detect the presence of the added determinism. As a control, the analysis was repeated, except that the added determinism was purely

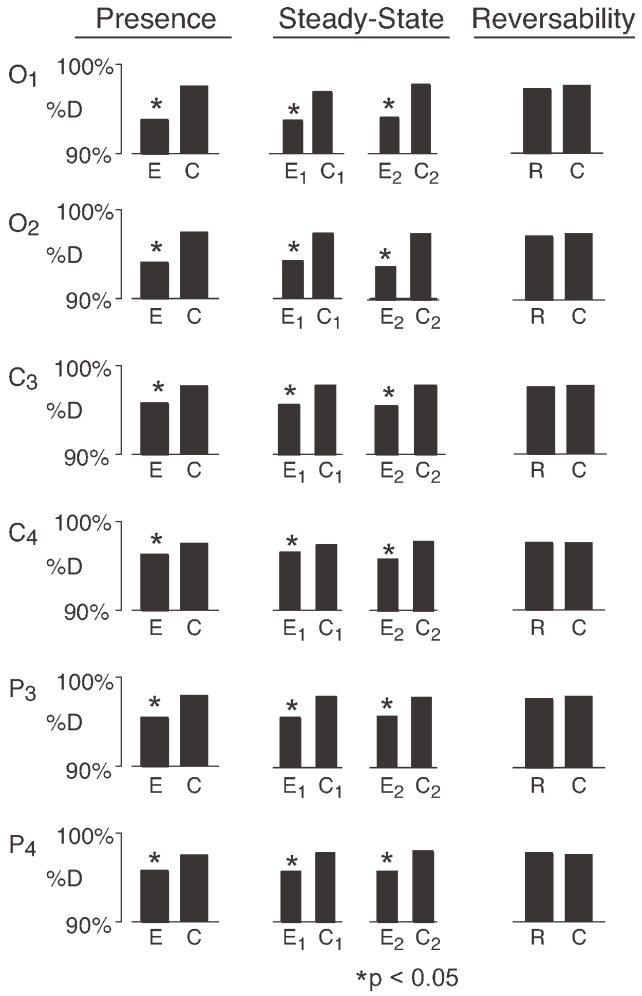

FIG. 3. Recurrence analysis of the effect of the magnetic field on the EEG from all derivations in subject S1. The standard errors are not resolved at the scale shown.

linear; this was accomplished by adding the sine waves such that their phases were identical in each trial (0° at t = 0.85 sec) (Fig. 4c, left column).

RESULTS

The steps in recurrence analysis of the EEG are shown in Fig. 2, using data from O_1 in subject S1. The recurrence plot for each epoch of interest in a given trial was computed (Fig. 2b) and %D was calculated (Fig. 2b, inserts). The process was repeated for all the trials, and the computed values were compared statistically (Fig. 2c–e). When the means of %D from the E and C epochs in all the O_1 trials from subject S1 were compared, a decrease in %D ($P < 0.05$) was found (Fig. 2c). When the corresponding segments of E and C were compared (E_1 versus C_1 and E_2 versus C_2 (Fig. 2a)), %D in each E segment was less ($P < 0.05$) than its control (Fig. 2d). Thus, the field-induced changes in brain activity were not localized within the 1-sec analysis interval, but rather occurred throughout the interval. The R versus C comparisons were not significantly different (Fig. 2e), indicating that the effect of the presence of the field on brain activity ended less than 2 sec after field offset.

We similarly analyzed the EEGs from the other five derivations in subject S1, and in each case %D in the E epochs was less ($P < 0.05$) than the corresponding C epochs (Fig. 3, first column). For each electrode derivation, when the E epoch was divided into bins of 500 ms and then compared with the corresponding bins of the C epochs, we consistently detected the effect of the field in both bins of the 1-sec interval (Fig. 3, second column), indicating that the change in brain activity was a steady-state phenomenon. The values of the determinism in the R epochs did not differ from the controls (Fig. 3, third column), indicating that brain electrical activity in subject S1 had returned to baseline within 2 sec after field offset. Linear analysis did not reveal a presence effect in the EEG from subject S1 (data not shown).

The analysis for subject S1 (Figs. 2 and 3) was repeated for the other 21 subjects, and a presence effect was detected in all subjects ($P < 0.05$ for ≥ 2 electrodes) except for S13 (Table 1). The effect was continuous over the 1-sec analysis interval in at least 18 subjects, as assessed on the basis of comparing segments in the E epochs with their controls (Table 1, bolded derivations). The R epochs did not differ significantly from the C epochs in any of the 21 subjects (data not shown).

Linear analysis yielded a presence effect only in subjects S9 and S13 (Table 1).

Table 1
Effect of the Presence of a Magnetic Field on Brain Electrical Activity Assessed by Recurrence Analysis (%D) and Time Averaging (V_{rms})*

Subject	%D	V_{rms}
S1 (50F)	**O1 O2 C3 C4 P3 P4**	—
S2 (29F)	**O1** C3 C4 **P3 P4**	—
S3 (18F)	O1 **C3 C4 P3 P4**	—
S4 (30M)	**O1 O2 P3 P4 C3 C4**	—
S5 (28F)	**O1 O2 C3** C4 **P3 P4**	—
S6 (30M)[a]	**O2 C3 C4 P3 P4**	—
S7 (45M)	**O1** O2 **C3 C4 P3 P4**	—
S8 (49F)	**O1 O2 C3 C4 P3 P4**	—
S9 (51M)	**O1 O2 C3** C4 **P3 P4**	O2 C4 P4
S10 (46F)	**O1 C3 C4 P3**	—
S11 (28F)	**O1 O2 C4 P3 P4**	—
S12 (44M)	**O2 P4**	—
S13 (20M)	—	C3 C4 P3 P4
S14 (33F)	**C4** P4	—
S15 (31M)	**O2 C3 C4** P4	—
S16 (32F)	O2 C4 P3	—
S17 (51M)	O1 **C3 C4 P3**	—
S18 (23M)	O2 **C4 P4**	—
S19 (18F)	**O1** O2 **C4** P3	—
S20 (21F)	**C4 P3 P4**	—
S21 (63F)	O1 O2 C4 **P3 P4**	—
S22 (62F)	**O1 O2** C3 C4 **P3 P4**	—

*Field strength 200 μT, except 100 μT for subjects S18–S22. For each subject, the derivations where a presence effect was found (pairwise significant at $P < 0.05$) are listed. Subjects with at least two pairwise significant derivations exhibited a presence effect (familywise error $P = 0.024$). Bolding indicates continuity of the effect throughout the 1-sec analysis interval. —, No effect. Age, gender shown in parentheses (F = female; M = male).

[a]False-positive detection (effects in C4 and P4 in the sham-exposure trials).

Table 2
Effect of the Presence of Sound on Brain Electrical Activity Assessed by Recurrence Analysis (%D) and Time Averaging (V_{rms})*

Subject	%D	V_{rms}
S1 (50F)	—	—
S2 (29F)	—	—
S3 (18F)	**O1** P3	—
S4 (30M)	C3 C4	C3 C4
S5 (28F)	O1 C3 C4 P3	O1 C3 C4
S6 (30M)	C3 C4 P3 P4	—
S7 (45M)	O1 O2 C3 C4 P3 P4	—
S8 (49F)	O2 C4 P3	C3 C4
S9 (51M)	—	—
S10 (46F)	—	—
S11 (28F)	—	O1 C3 C4 P3 P4
S12 (44M)	C3 C4	C3 C4 **P4**
S13 (20M)	**C3 C4 P3 P4**	O1 O2 P3 P4
S14 (33F)	—	**O1 O2 C3** C4 P3 P4
S15 (31M)	—	O1 O2 C3 C4 P3 P4
S16 (32F)	C3 C4 P3	—
S17 (51M)	—	C4 P3
S18 (23M)	—	C3 C4
S19 (18F)	C3 P3 P4	O1 C3 C4 P3 P4
S20 (21F)	—	—
S21 (63F)	—	—
S22 (62F)	—	—

*For each subject, the derivations where a presence effect was found (pairwise significant at $P < 0.05$) are listed. Subjects with at least two pairwise significant derivations exhibited a presence effect (familywise error $P = 0.024$). Bolding indicates continuity of the effect throughout the 1-sec analysis interval. —, No effect. Age, gender shown in parentheses (F = female; M = male).

A presence effect due to the sound stimulus was found in 10 subjects, using recurrence analysis, and 11 subjects, using time averaging (Table 2). The effect was reversible (R versus C comparisons not statistically significant) in all cases (data not shown) and not continuous except for subjects S13 and S14 (Table 2).

Addition of random-phase sine waves to successive trials of EEG (which mimicked a nonlinear stimulus-response relationship) was detected by nonlinear analysis, but not by time averaging (Fig. 4b). When the added signal always had the same phase (consistent response, which entailed a linear system), the added determinism could be detected by both time averaging and recurrence-plot analysis (Fig. 4c), as expected.

DISCUSSION AND CONCLUSIONS

The magnetic fields used in MRI have historically been termed noninvasive; nevertheless, they penetrate throughout the body and give rise to electric fields that are also pervasively present. If these magnetic and/or electric fields altered the electrical activity of the brain, then the BOLD response due to task-related cognitive activity might be confounded with a direct response caused by the fields. We tested the hypothesis that a magnetic field having a frequency and strength comparable to one of the fields present during MRI induced steady-state changes in brain electrical activity during the time the field was present in the subject's environment.

Using nonlinear analysis, we found that the magnetic field caused a steady-state change in brain electrical activity in 21 of 22 subjects (Table 1). Several considerations supported the reliability of these results. First, the condition taken to indicate a change in brain activity ($\geq$2 of six electrodes pairwise significant at $P < 0.05$) had an associated familywise error of $P < 0.024$; thus, the presence effect could not be explained by chance. Second, the possibility of an unrecognized systematic bias in the mathematical calculations could be excluded because the same calculations were made using the EEG recorded during sham trials, and only one case of false-positive detection occurred (Table 1, subject S6). Third, the changes occurred 0.5–1.5 sec after the field had been applied; their latency ruled out the possibility they were generated by a field-electrode interaction (a process that has no latency) or evoked potentials (which decayed within 0.5 sec). Fourth, studies using phantoms of the human head verified that the well-known artifacts associated with EEG measurements during application of magnetic fields (13) could not have affected our results because (1) the signal analyzed contained no spike artifacts such as occur at field onset or offset; (2) the EEG contained no Fourier component at the frequency of the magnetic field (zero EEG power >35 Hz, due to filtering); and (3) using phantoms, we estimated that neither electrode motion nor ion flow was capable of producing a detectable signal. The observed effects were therefore probably not due to the presence of 60-Hz energy nor to a signal derived from non-neuronal sources. Fifth, the R versus C comparisons (Fig. 2a) did not differ significantly in any of the subjects, indicating that baseline

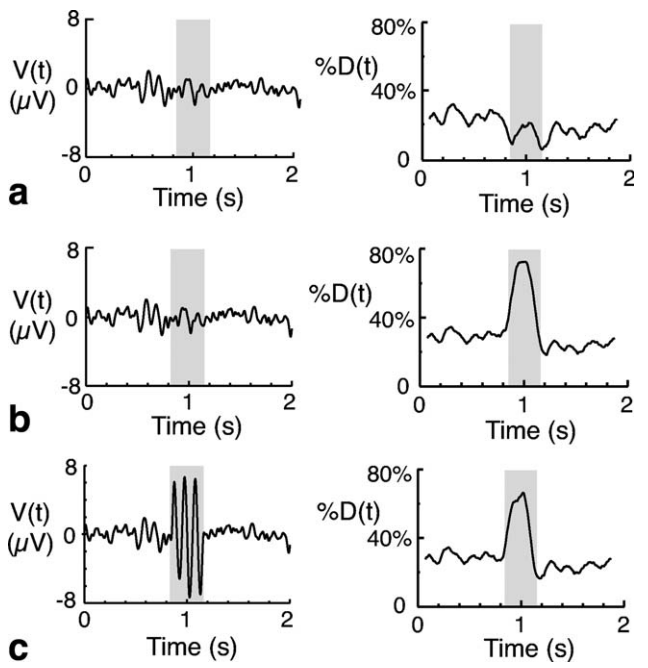

FIG. 4. Detection of known determinism using nonlinear and linear analysis. **a:** Time average of 50 baseline EEG trials and of the corresponding %D(t) time series. **b**,**c:** Effect of addition of random-phase (0–360°) and fixed-phase (0°) 10-Hz sine wave to each trial, respectively. The signals were added at t = 0.85–1.15 sec (stippled).

EEG behavior was reestablished within 2 sec of field offset.

Finally, in 79% of the derivations where a presence effect was found, we demonstrated ($P < 0.05$) that it occurred in both halves of the E epoch (the 76 bolded entries in Table 1 [out of 96]). Similar results occurred when E was divided into thirds (333-ms bins) and compared with the corresponding intervals in C (data not shown). Thus, in the sense defined above (see Materials and Methods) the effects on brain dynamical activity (Table 1) were steady-state effects because they persisted continuously during the period of application of the cognate MR field and ceased after its removal.

The precise location of the analysis interval (0.5–2 sec, possible range) was not critical (data not presented), suggesting that the presence effect occurs for periods even longer than those considered here. We previously described the existence of an onset evoked potential that lasted about 250 ms and occurred at 100–500 ms after stimulus onset (depending on the subject) (9). The novel aspect of our present findings involved the duration and latency of the effect; its relationship to the onset evoked potential, if any, remains unknown.

Using time averaging, a field-induced presence effect was found in only two subjects (S9, S13) (Table 1). Linear methods (time averaging, spectral analysis, general linear models, as examples) are ideal for detecting linear stimulus-response relationships but are far less efficient when the relationship is nonlinear because they capture only a linear approximation of the dynamical activity.

Nonlinear analysis detects both linear and nonlinear determinism, whereas linear analysis detects only linear determinism. When an analysis is positive using nonlinear methods but negative using linear methods, the implication is that the determinism was nonlinear only; this was the case for the field-induced effect (found in all but one subject using nonlinear analysis but not found using linear analysis; Table 1). When both methods yield essentially the same results, the most parsimonious implication is that the determinism was linear; this was the case for the sound-induced effect where about half the subjects detected the field using either method (Table 2). However, all of the subjects actually heard the sound, thus raising the question of why recurrence analysis was less efficient in detecting a presence effect whose validity could be independently established by simply interviewing the subjects. One possibility was that the phase-space and recurrence parameters used in the analyses, which were chosen previously to detect field-induced changes (9,24), were stimulus specific. For example, the effect of sound was detected more efficiently using a lower time delay than used here (9). Moreover, %D is only one of several recurrence variables (22). Given a specific set of phase-space and recurrence parameters, the mathematical algorithm for calculating one recurrence variable may be more efficient than that for calculating another.

Recurrence plots were designed to reveal patterns in mathematical equations (21). Zbilut and Webber (22) recognized that this principle also applied to physiologic time series; they introduced the concept of quantifying the plot and showed that %D was a useful measure of law-governed activity. The meaning of *changes* in %D in the EEG is more problematical because %D itself consists of aperiodic nonstationary determinism from numerous interacting brain regions (only some of which were involved in the cognitive representation of the field) inextricably mixed with noise. There is no evidence suggesting that the incremental change in %D produced by the field originated in the same brain region or for the same reason in different subjects. The practical consequence is that although recurrence analysis can reliably be used to assess whether two sets of time series obtained from a subject under different conditions differed from each other, it is presently not possible to pinpoint the physical or physiologic process that gave rise to the difference.

The effects were robust, as evidenced by our ability to detect them in almost all of the subjects (Table 1). Furthermore, they were detected in a model-independent manner in the sense that we made no hypotheses regarding *how* the magnetic field affected the dynamical activity of the brain. Our detection method (phase-space embedding) employed the canonical approach for analyzing nonlinear systems and was quantitated using recurrence analysis, which is particularly effective in the evaluation of nonstationary biologic time series.

The results exhibited no clear electrode topographical pattern or dependence on field strength (Table 1), which, it might be argued, is counterintuitive. However, the expectation that the data *ought* to be consistent with regard to topography or dependence on field strength is based on an implicit assumption that the relationship between stimulus presentation and brain-activity changes was governed by linear dynamical laws. But this relationship must be determined empirically, not by assumption. Using an analytical method appropriate for a linear model (time averaging), we found field-induced effects in two subjects. In contrast, when the data were examined using a method tailored for a nonlinear model, effects were found in 21 of 22 subjects. Not surprisingly, the characteristics of these effects were those expected for a nonlinear system, rather than those expected for a linear system (consistent scalp location and proportionality to field strength). Looked at another way, our results provided no evidence suggesting that the magnetic fields produced linear changes in brain electrical activity. On the other hand, the results provided good evidence that they actually altered brain electrical activity in most of the subjects and that the stimulus-response system was governed by nonlinear dynamical laws.

Prior studies of the effects of magnetic fields on brain electrical activity employed linear analysis (25,26), despite the complexity of the brain (6,14–18). The mismatch between the nature of the brain's dynamical activity and the methods used to analyze the field-brain interaction could explain why the ability of magnetic fields to produce steady-state changes in brain electrical activity had not been reported previously. Previous fMRI/EEG studies used typical EPI conditions and employed linear analysis techniques. Consequently, it was not possible to analyze for a presence effect because there was no reasonable time period (say, 1 sec) during

which a specific magnetic field was applied and the EEG was recorded and analyzed in relation to the application of the field. Our experimental design was novel in this regard.

The nonlinear analysis method used here, recurrence analysis (22), encompasses other quantifiers in addition to %R and %D, and other nonlinear processing methods have been described (27–29). The relative sensitivity and utility of other quantifiers and processing approaches have not been determined.

Our goals here did not involve improving understanding of mechanisms in fMRI. Previously, we described animal studies suggesting that the electroreceptor cell was located in the head, possibly the cerebellum (30,31). The actual transduction process may involve ion channels having field-sensitive gating characteristics (32).

Repetitive transcranial magnetic stimulation also produces complex changes in brain electrical activity (33), but the effects differ fundamentally from those described here. For example, repetitive transcranial magnetic stimulation effects occur *after* stimulation and persist following its termination (34), whereas the effects we reported occurred *during* stimulation and rapidly (2 sec) disappeared when stimulation ceased (Table 1). Also, repetitive transcranial magnetic stimulation occurs in any axon where the induced depolarization exceeds that needed to trigger an action potential. In contrast, the magnetic field studied here was detected by sensory transduction mediated by a force transducer (32) in specialized cells, possibly located in the cerebellum (30), not by the action-potential-generating mechanism consisting of Na^+ and K^+ channels found in excitable cells (35). Finally, the repetitive transcranial magnetic stimulation magnetic field (0.5–3.5 T, pulse width 400 μs (Magstim, Carmarthenshire, Wales, UK)) produces induced electric fields that far exceed in strength those associated with the magnetic field we studied (or with the non-zero-frequency fields associated with fMRI).

It might be argued that sinusoidal gradients of 100–200 μT, 60 Hz, do not mimic a typical EPI acquisition for fMRI. For example, assuming a bandwidth of 100 kHz, a field of view of 60 cm, a head diameter of 16 cm, and a readout time of 50 ms, at 1 T, 42 MHz, the field would be about (100 kHz/0.6 m)(1 T/42 MHz)(0.16 m) $\cong$ 600 μT at a frequency of 64 cycles/50 ms = 1200 Hz. Nevertheless, a Fourier decomposition of the field in the example (or in essentially any EPI acquisition) contains energy at 60 Hz. Although 60 Hz was too slow to represent EPI gradients, thereby preventing a direct interpretation of our results in terms of an actual simulation, our approach permitted an interpretation in terms of the basic issue of whether fields produce steady-state effects, which was our goal. We assumed that effects at 60 Hz, 200 μT would raise a reasonable possibility of effects occurring at other frequencies in the subradiofrequency band (below about 3000 Hz), 1200 Hz, for example, and at stronger fields. Moreover, the present evidence suggests that the body transduces the induced electric field, not the magnetic field (32). The strength of the induced field is proportional to frequency and would therefore be greater at 1200 Hz compared with 60 Hz.

How do the results described here apply to fMRI? Assume a conventional cognitive comparison strategy involving a block design, acquisition of time-series data, calculation of a test statistic, formation of individual activation and difference maps, and determination of group activation maps (5,36). A key implicit assumption is that the signal-to-noise ratio of the BOLD responses increases with the number of scans, which is a fundamental property of a linear dynamical system (Figs. 4b and c, left panel). But nonlinear systems behave quite differently; in particular, their responses to stimuli can be inconsistent from trial to trial. The BOLD signal recorded after a cognitive stimulus might differ from trial to trial because of the inconsistent (nonlinear) direct effect of the magnetic field on the cells of the brain. The implications with regard to the functional connectivity inferred from the scans depend on the analytical techniques used to evaluate the data. Linear analysis detects only linear changes, so the effect would be averaged away (Fig. 4b, left panel). Nonlinear analysis, in contrast, detects any kind of law-governed activity (Fig. 4b and c, right panels).

Use of group-averaged brain activation maps in functional MR studies entails the assumption that different subjects reacted similarly; only linear systems exhibit that kind of consistent behavior (in nonlinear systems, the signal-to-noise ratio typically decreases when results are averaged across subjects). The ability of magnetic fields to induce changes in brain activity would therefore not be expected to affect group-averaged brain-activation maps, with the possible exception of adding noise to the data. On the other hand, study designs that block on the individual rather than the group (thereby allowing for effects that are inconsistent from subject to subject) might generate insights not obtainable using linear techniques. The existence of a dynamically nonlinear field-induced contribution to the BOLD responses and whether they constitute an additional limitation of the methodology (37) are empiric issues to be resolved by future studies.

The salient characteristics of the effect we described were its nonlinearity and its steady-state property. As defined above, "steady state" meant that the brain activity during the analysis interval was statistically distinguishable from the control. Nevertheless the field-induced change was not constant in the sense that it could be averaged away or removed by subtraction. The effect would be expected to occur in both task and nontask states, but there is no basis to assume the effects would be identical or would occur in the same regions in the brain. Indeed, because the effect is nonlinear, the expectation would be that it would differ between task and nontask states (because the dynamical activity of a nonlinear system depends on its initial state, which is not true for a linear system). This is the central reason that, depending on the fMRI study design, purpose, and data analysis techniques, it may be necessary to take into consideration the effect of the field on brain activity in interpreting the data.

In general, to decide whether a nonlinear effect is really a significant confound one could devise modifications of the experimental and statistical plans

specifically geared to test the hypothesis. Alternatively, it may be possible to retain the experimental plan and augment the statistical plan to include a form of analysis that is sensitive to nonlinear phenomena. A simpler approach may give an investigator an indication regarding whether a prospective investigation of the issue is warranted. Typically, in a linear analysis, the prototypical indication of a nonlinear confound is an unexpected variance in the variance of the data subsets. The effect arises because the direction of a nonlinear effect is inconsistent from trial to trial, as assessed, for example, using the F test (38).

In summary, EEG measurements in a simulated MRI field environment indicated that the field produced nonlinear steady-state changes in brain electrical activity in 21 of 22 subjects, suggesting that scanner fields could also alter brain electrical activity. The implication is that, depending on the experimental design, the interpretation of functional MR images could be affected if, as seems reasonable, the effects are reflected in the BOLD responses. However, the results do not necessarily mean that fundamental brain connectivity is altered during an fMRI experiment, but rather that further exploration of the issue is needed.

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