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The discrepancy between human peripheral nerve chronaxie times as measured using magnetic and electric field stimuli: the relevance to MRI gradient coil safety

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Abstract

Peripheral nerve stimulation (PNS) resulting from electric fields induced from the rapidly changing magnetic fields of gradient coils is a concern in MRI. Nerves exposed to either electric fields or changing magnetic fields would be expected to display consistent threshold characteristics, motivating the direct application of electric field exposure criteria from the literature to guide the development of gradient magnetic field exposure criteria for MRI. The consistency of electric and magnetic field exposures was tested by comparing chronaxie times for electric and magnetic PNS curves for 22 healthy human subjects. Electric and magnetic stimulation thresholds were measured for exposure of the forearm using both surface electrodes and a figure-eight magnetic coil, respectively. The average chronaxie times for the electric and magnetic field conditions were 109 ± 11 μs and 651 ± 53 μs (±SE), respectively. We do not propose that these results call into question the basic mechanism, namely that rapidly switched gradient magnetic fields induce electric fields in human tissues, resulting in PNS. However, this result does motivate us to suggest that special care must be taken when using electric field exposure data from the literature to set gradient coil PNS safety standards in MRI.

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Introduction

Magnetic field gradient coils are a necessary component of every MRI system, and their operation in many ways determines overall imaging performance. The acquisition of high-resolution images in relatively short times, while maintaining the ability to generate versatile image contrast, requires the freedom to produce large maximum gradient strengths in small switching times. Throughout the history of the development of modern MRI systems, the performance of the gradient system has steadily and significantly improved.

There is a major problem inherent in the operation of gradient coils at high strengths and speeds. Magnetic gradient fields that vary rapidly in time induce electric fields that, if large enough, can cause peripheral nerve stimulation (PNS) in human subjects (Schaefer *et al* 2000). This effect is sometimes referred to as magnetostimulation, but in this paper it will be referred to as magnetic field PNS or simply PNS. Advances in gradient amplifier technology over the past decade have made PNS much more common, and the onset of this effect currently marks the upper limit on gradient system operation. This phenomenon was initially reported in humans by Cohen *et al* (1990), and it has since been a topic of active research as reviewed by Schaefer *et al* (2000).

PNS is not considered to be particularly dangerous on its own. At threshold levels, PNS typically manifests itself as a light vibration or poking sensation in the skin. At levels approximately 50% higher than threshold, the sensations become painful. However, the PNS threshold level is important in MRI because it is currently considered an early-onset indicator of the presence of induced electric fields that have the potential for more serious consequences. In particular, stimulation of vital organs and tissues within the body, such as the diaphragm or the heart, is of primary concern. For the temporal frequencies typically used in MRI gradient systems (the low kHz range), the thresholds for respiratory and cardiac stimulation are respectively one and two orders of magnitude larger than thresholds for PNS (Reilly 1998). By setting operational limits on commercially available gradient systems below the levels required to induce PNS, the possibility of inducing dangerous stimulation is reduced to a negligible level. A critical goal in gradient system development is to understand the factors influencing PNS thresholds sufficiently well that gradient system performance can be maximized without exposing subjects to undue risk.

There exists a wealth of literature in which the characteristics of direct electrical stimulation of human nerves are studied, and these are well summarized in the textbook by Reilly (1998). Since the basic model of magnetic stimulation by MRI gradient coils is simply magnetically induced electric stimulation of the nerves, it should be possible to take advantage of this literature and translate it into terms relevant to MRI gradient coil exposure conditions. In fact, it is this basic hypothesis that has motivated the use of electric field exposure criteria from the literature to guide the establishment of magnetic field exposure criteria in MRI (Athey 1992, International Electrotechnical Commission (IEC) 2001). Specifically, gradient coil stimulation thresholds have been expressed in terms of nerve stimulation parameters obtained directly from electric field exposure studies (Athey 1992).

The electric field required for stimulation of a peripheral nerve, E_{stim}, experienced for a time duration, τ, is well approximated by the following strength–duration relationship (Irnich and Schmitt 1992):

$$E_{\mathrm{stim}} \geqslant E_r \cdot (1 + \tau_c/\tau). \tag{1}$$

Here, E_r is known as the electric field rheobase and is defined as the minimum electric field required for stimulation of a nerve under conditions of constant exposure. The chronaxie time, τ_c, is the electric field pulse duration for which the stimulation threshold is twice the rheobase value. Physiologically, the chronaxie time is indicative of the time needed to induce nerve depolarization. Once an electric field threshold curve is measured as a function of τ, equation (1) can be fit to the threshold curve and the two parameters determined.

The above *E*-field threshold curve can be recast into an equivalent form for magnetic field exposure (Irnich and Schmitt 1992, Chronik and Rutt 2001b, Bourland *et al* 2001, appendix A):

$$\Delta B_{\text{stim}} \geqslant \left(\frac{\mathrm{d}B}{\mathrm{d}t}\right)_{\text{min}} \cdot \tau + \Delta B_{\text{min}} \tag{2}$$

where ΔB_{stim} is the total change in the magnetic field required to cause stimulation when switched over a time τ. ΔB_{min} is the minimum change in the magnetic field necessary to cause stimulation in the limit of an infinitely high $\mathrm{d}B/\mathrm{d}t$, and $(\mathrm{d}B/\mathrm{d}t)_{\text{min}}$ is the minimum rate of change in the magnetic field required to cause stimulation in the limit of high magnetic fields. The chronaxie time for magnetic field PNS can be obtained directly from measurement of the magnetic stimulation threshold parameters (Chronik and Rutt 2001a, appendix A):

$$\tau_c = \Delta B_{\text{min}} \Big/ \left(\frac{\mathrm{d}B}{\mathrm{d}t}\right)_{\text{min}}. \tag{3}$$

It should be noted that τ_c is calculated directly from the shape of the stimulation curve, independent of any induced electric field calculations. The rheobase value (E_r) cannot be obtained from the curve parameters alone, but requires an accurate total electric field calculation in order to be determined. In this work, E_r is not considered and only τ_c values are compared between electric and magnetic field exposure conditions.

Other researchers have directly compared electric and magnetic stimulation in human subjects, but not in terms of chronaxie time. Olney *et al* (1990) evaluated the clinical utility of magnetic coils compared to standard electric stimulation. They compared the two modes of stimulus by measuring the effect of stimulus intensity on the amplitude of a nerve response. They reported that nerve responses elicited electrically and magnetically during nerve conduction studies were similar but with subtle differences. A similar study was conducted by Amassian *et al* (1989), where they compared the ulnar nerve response for both magnetic and electrical stimulation. No strength–duration relationships were measured as they focused specifically on the orientation of the magnetic coil; therefore, no chronaxie time values could be extracted.

The goal of this work was to experimentally obtain both electric and magnetic field PNS threshold curves for a group of normal human volunteer subjects, and to determine the extent to which the respective chronaxie times are consistent. The primary mechanism of gradient-induced PNS as outlined above was not in question in this work. Only the possibility of a consistent discrepancy in the measured nerve chronaxie times was under investigation. As is reported in detail below, the basic result obtained using the methods of this study is that the electric and magnetic field PNS chronaxie values are significantly different.

Methods

This study was approved by The University of Western Ontario Research Ethics Board for Health Science Research Involving Human Subjects (2005). Twenty-two normal healthy subjects (15 males and 7 females) participated in this study. The mean and standard deviations for age, weight and height of the subjects were 23.5 ± 6.4 years, 70.9 ± 11.7 kg and 173.8 ± 7.6 cm, respectively. None of the subjects displayed any obvious anxiety during the experimental protocol. Each subject was studied during a single session that involved

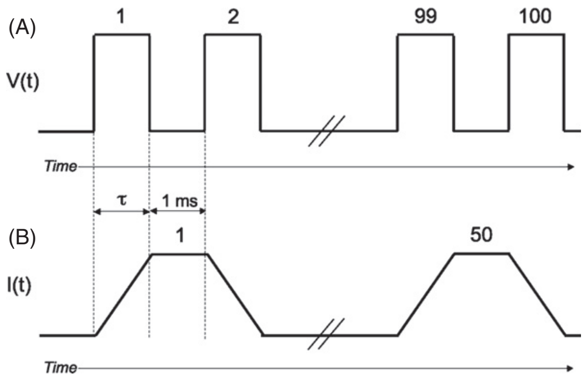

Figure 1. Illustration of the electric stimulation waveform (A) and the corresponding magnetic stimulation waveform (B) as a function of time. Each pulse in the electric waveform and rise time in the magnetic waveform has a time duration, τ, which are separated by a plateau time of 1 ms. The electric waveform consists of 100 pulses, and the magnetic waveform consists of 50 trapezoidal lobes.

separate electric and magnetic stimulation phases, with the entire session lasting approximately 120 min. The order in which the phases were conducted was randomized across all subjects.

Electric stimulation

A Grass-Telefactor Model S48 electric stimulator (Astro-Med Inc., Longueuil, Quebec) was used for all electric stimulation experiments. The stimulator consisted of a pair of 0.8 cm diameter circular electrodes separated by 2.9 cm (center to center). The stimulator output impedance was set to 25 Ω resulting in a constant voltage output source. The applied electric field waveform was monitored during all experiments using an oscilloscope and no significant distortions from the expected waveform were observed. No electrical conductive gel was utilized because its use changes the effective size of the contact area of the electrodes producing variability within the subjects (Pfeiffer 1968). All threshold measurements were taken at room temperature. The waveform (figure 1(A)) was a sequence of 100 monophasic rectangular electric field pulses. Each pulse in the waveform was separated by 1 ms. The duration (τ) of each pulse in the waveform was set to a value between 100 and 1000 μs. The repetition rate of the pulse train was 1 Hz.

The electric pulse generator was capable of producing only monophasic pulse trains, whereas any magnetic waveform must always induce a biphasic electric field pulse train. Experiments and simulations (Reilly *et al* 1985) have shown that biphasic electric pulse trains have higher excitation thresholds than monophasic pulse trains; however, these studies also showed that as the time delay between pulses is increased, the difference between monophasic and biphasic pulse trains decreases. For pulse separations of approximately 1 ms and larger, there is no significant difference observed. This is the rationale for the 1 ms separation in the waveform used in this study. The relative refractory period of a single action potential in a peripheral nerve is in the order of 1 ms. Therefore, within 1 ms, the potassium permeability is decreased such that the membrane potential is very close to its resting potential before the next mono/biphasic pulse within the waveform sequence stimulates.

The electrodes were placed on the distal, anterior surface of the forearm between the tendons of the palmaris longus and flexor carpi radialis (figure 2(A)). The electrodes were

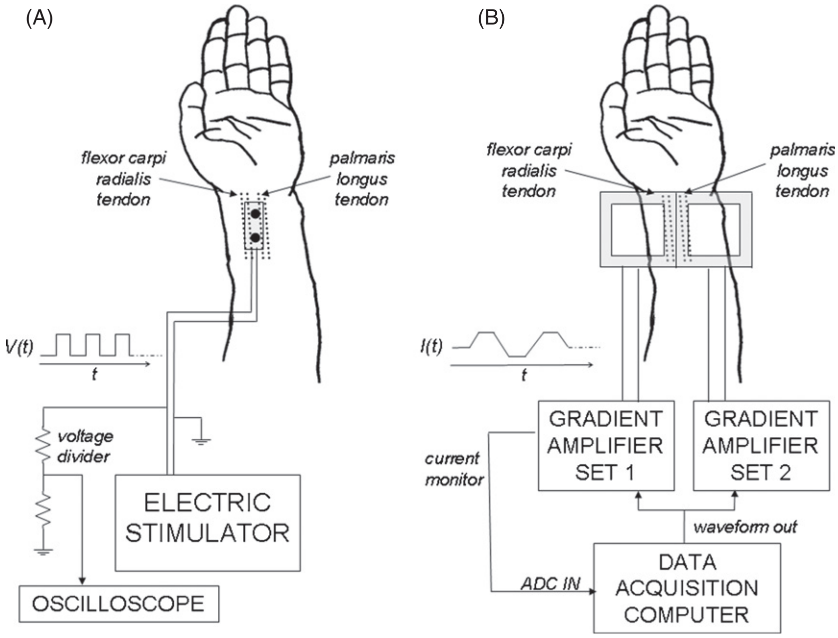

Figure 2. Equipment setup for the electric stimulation experiment (A) and the magnetic stimulation experiment (B). For the electric stimulation experiment, stimulating surface electrodes were placed on the distal, anterior surface of the forearm between the tendons of the palmaris longus and the flexor carpi radialis. The voltage waveform was produced by the electric stimulator and was read by the oscilloscope. The magnetic coil was placed in the same position. The data acquisition computer produced and monitored the current waveform that was supplied to the gradient amplifiers. One pair of gradient amplifiers supplied current to each lobe of the coil.

placed such that the electric field direction was parallel to the expected orientation of the underlying nerves. At the start of the experiment, subjects were allowed to become familiar with the sensations of electrode stimulation.

Electric field threshold curve measurements were made as follows. A value of τ was chosen randomly between 100 and 1000 μs (in allowable increments of 100 μs). The subjects were allowed to control the stimulator voltage directly. The threshold for perception was defined as the minimum voltage at which any sensation or muscular contraction occurred, as determined by the subject. The voltage across the electrodes at the threshold reported by the subject was measured and recorded directly from the oscilloscope. This process was repeated for randomly chosen τ values within the specified interval producing a threshold strength–duration curve. A total of 44 separate measurements were made, corresponding to four separate threshold measurements of each τ value, all in a random order. The average threshold at each τ value was taken to be the mean of the four measured values, with an uncertainty given by the standard deviation in the measured values.

Magnetic stimulation

A ‘figure-eight’ coil design was constructed for magnetic stimulation (Evans 1991). The full coil consisted of two square cross-section, square wound coils placed side by side, with opposite relative current direction. The inner length of each coil was 5 cm and was wound using

12 AWG round copper magnet wire. Each section of the coil consisted of 81 windings, arranged 9 by 9 resulting in an inductance of 1170 μH for the assembly. The dc resistance for each coil section was 0.168 Ω, which increased to 0.402 Ω at 1 kHz. The coils produced a magnetic field of 0.825 mT A^{-1} at a position 1.2 cm above the center of the coil assembly. To reduce heating, the coil was completely potted within a high thermal conductivity epoxy compound (Cotronics Corp., Durapot^{TM} 865 Epoxy, Brooklyn, New York). Copper refrigeration tubing for forced water cooling (6 $^\circ$C) was also built into the system. The final structure was 26 cm by 18 cm and 16 cm deep, and weighed 10.6 kg.

The current waveform was produced by four Techron Model 8607 amplifiers (GE Medical Systems, Milwaukee, WI, USA). Two amplifiers operating in master-slave mode were independently connected to each coil lobe, and simultaneously driven with identical waveforms. The amplifiers were operated in current mode, producing peak currents of $\pm$125 A. The maximum current slew rate for the configuration was 439 kA s^{-1}, which corresponds to a switching time from minimum current ($-$125 A) to maximum current (+125 A) of 570 μs. The duty cycle was limited to 12% by temperature rise within the coil, resulting in an average power deposition of 183 W.

The magnetic field pulse waveform (figure 1(B)) was trapezoidal, with a flat-top duration of 1.0 ms and a variable switching time (τ) ranging between 100 and 1000 μs. Each waveform consisted of 50 alternating trapezoidal pulses. The flat-top duration corresponds to the separation between induced electric field pulses, and 1 ms flat-top duration is therefore consistent with the 1 ms separation between pulses used for the electric field stimulation. The applied current waveform was monitored during all experiments and no significant distortions away from the expected trapezoidal waveform were observed. The waveform was monitored by measuring the current supplied to the magnetic coils using the data acquisition computer. Since the frequency of the applied current waveform was in the kHz range, the quasi-static approximation holds and no significant wavelength effects are expected and the waveform of the induced electric field within the tissue can be assumed to be proportional to the time derivative of the applied magnetic field waveform (Roth *et al* 1991).

The forearm of the subject was positioned over the coil so that the peak-induced electric field was over the same location (distal, anterior surface of the forearm between the tendons of the palmaris longus and flexor carpi radialis) and was in the same direction (parallel to the underlying nerves) as for the electric measurements (figure 2(B)). Subjects were first allowed to familiarize themselves with the sensation(s) invoked by the magnetic coil. For the stimulation threshold curve measurements, a value of τ between 100 and 1000 μs was chosen randomly from the same set of pulse durations used during the electrical stimulation experiment. The total change in the magnetic field was varied up and down until the threshold was determined. The threshold for perception was defined as the minimum change in the magnetic field that resulted in any sensation or muscular contraction as perceived by the subject. This procedure was repeated for all remaining values of τ.

Analysis

For electric stimulation threshold measurements, equation (1) was fit to the data from each subject using a least-squares method to obtain an electric field chronaxie time for each subject. For the magnetic stimulation threshold measurements, equation (2) was fit to the data from each subject using a least-squares method to obtain both ΔB_{min} and $(\mathrm{d}B/\mathrm{d}t)_{\mathrm{min}}$ values for each subject. The corresponding magnetic field chronaxie time was then calculated for each subject from equation (3). Calculation of the chronaxie time is theoretically independent of the magnetic field strength, as shown in appendix A. The mean, median, standard deviation

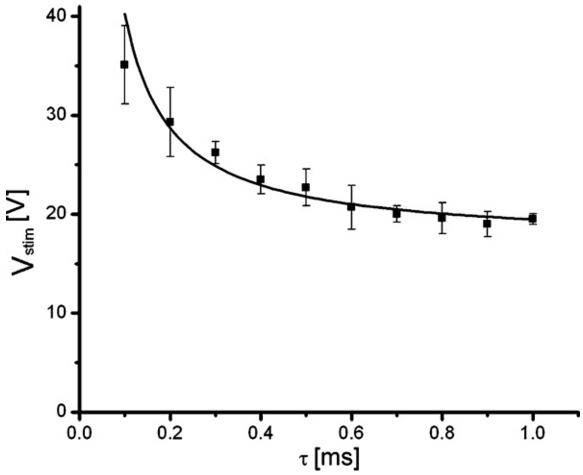

Figure 3. Example subject electric stimulation threshold curve. V_{stim} represents the electric stimulation threshold. The τ_c for this subject was 134 ± 23 μs. Error bars indicate ±1 standard deviation for all four measurements taken at each τ. The r^2 for this fit to equation (1) was 0.92, demonstrating the high degree to which the measurements for an individual subject complements the electric strength–duration relationship.

and standard error in the mean were calculated from the samples of chronaxie time from each of the electric and magnetic field exposure populations. The correlation coefficient for the electric and magnetic chronaxie times was also calculated. A paired two-tailed Student's *t*-test was used to test for significance in the difference between the two means.

Results

All 22 subjects reported stimulation during the electric stimulation phase of the experiment. Subjects qualitatively described sensations (from most to least common) as 'prickling', 'pulsing', 'burning', 'buzzing' or 'throbbing'. All subjects reported the primary location of the sensations to be directly underneath the electrodes. One subject reported an additional muscular contraction more proximal on the forearm, and one reported an additional sensation in digits III and IV. Nine subjects reported that the sensation for pulse durations shorter than 100 μs was a softer, pulsing sensation, as compared to the longer duration pulses.

Twenty-one of the 22 subjects reported stimulation during the magnetic stimulation phase of the experiment. The most common description of the sensation was 'tingling', which was reported by 12 subjects. Other descriptions included 'vibrations', 'twitching', 'buzzing' or 'numbness'. All subjects described the sensation as originating distal to the stimulator location, either in the palm, digits or both. Seven subjects reported stimulation throughout the palm of the hand. Eight reported stimulation only in digits I, II, III and IV, or the medial three digits. Six reported stimulation only in digits IV and V or only digit V. One subject reported stimulation only in digit IV. Five subjects reported stimulation throughout all digits.

Electric stimulation thresholds for a single subject are shown in figure 3. Each data point is the mean threshold over the four measurements at that specific τ. Error bars are ±1 standard deviation as estimated from the four measurements. The electric field chronaxie time obtained for this subject was 134 ± 23 μs ($r^2 = 0.92$). Magnetic stimulation thresholds for the same subject are shown in figure 4. Each data point is a single measurement for the

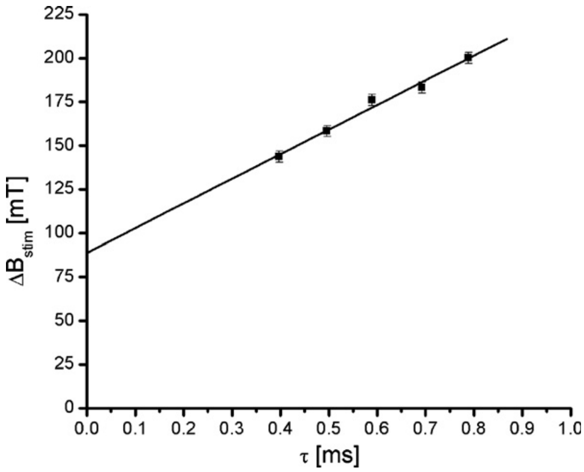

Figure 4. Example subject magnetic stimulation threshold curve (same subject as in figure 3). A fit of theses measurements to equation (2) yields a τ_c of 631 ± 91 μs. Error bars indicate ±1 standard deviation, which is estimated from the threshold measurements and the results of the fit. The r^2 for this fit to equation (1) was 0.98, demonstrating the high degree to which the measurements for an individual subject complements the magnetic strength–duration relationship.

threshold. The error bars were derived from the results of the fit of equation (2) to the data. The stimulation threshold for $\tau < 0.4$ was not attainable for this particular subject because the gradient amplifier configuration was limited by the maximum slew rate. The magnetic field chronaxie time obtained for this same subject was 631 ± 91 μs ($r^2 = 0.98$). For the electric stimulation chronaxie times, there was no significant difference between the male and female subjects ($P = 0.636$). There was also no significant difference between the male and female subjects for the magnetic chronaxie times ($P = 0.416$).

Dot diagrams of the distributions of electric and magnetic τ_c are shown in figure 5. There were two outliers, discussed at the end of this section that are not shown in the figure or included in the results of this paragraph; therefore, the following results are for a paired sample of 20 subjects. The mean electric τ_c was 109 ± 11 μs and the median value was 97 μs. The r^2 value for the electric field subject fits ranged from 0.54 to 0.98 with a mean (median) value of 0.82 (0.84). The mean magnetic τ_c was 651 ± 53 μs and the median value was 595 μs. The r^2 value for all magnetic field subject fits ranged from 0.73 to 1.0 with a mean (median) value of 0.93 (0.96). The uncertainty for the mean chronaxie times indicates ±1 standard error in the estimation of the mean. The 542 μs difference between the mean electric and magnetic τ_c was found to be highly significant ($P < 0.001$). The sample correlation coefficient, r, between the electric and magnetic τ_c was 0.06. In figure 6, the values of the electric and magnetic τ_c for each subject are plotted against each other. For all subjects, the magnetic τ_c was much higher than the electric τ_c.

Of the two outliers in the study, the first individual had a poor fit ($r^2 = 0.14$) of equation (1) to his or her electric stimulation thresholds, and yielded a chronaxie time of 14 μs. The other subject also had a poor fit ($r^2 = 0.38$) to the electric stimulation model yielding a chronaxie value of 22 μs, but also did not stimulate from the magnetic coil within the capabilities of equipment used in this experiment. Both subjects appeared notably confused during the experiment. When including the chronaxie times for these two subjects, the mean electric τ_c becomes 100 ± 12 μs, and the mean magnetic τ_c becomes 655 ± 51 μs. The 555 μs

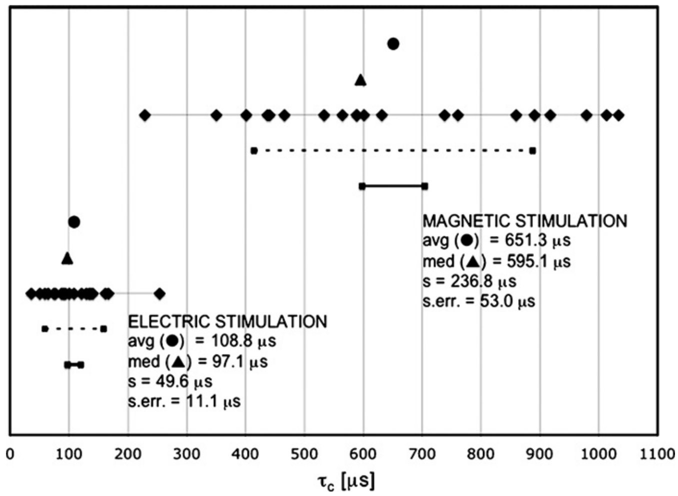

Figure 5. Dot diagram comparing electric and magnetic τ_c distributions. Diamonds represent the τ_c for a single subject. The circle indicates the mean τ_c for each respective mode of stimuli. The triangle indicates the median. The dashed bar indicates the value of ± 1 standard deviation about the mean. The solid bar indicates the value of ± 1 standard error in the estimation of the mean.

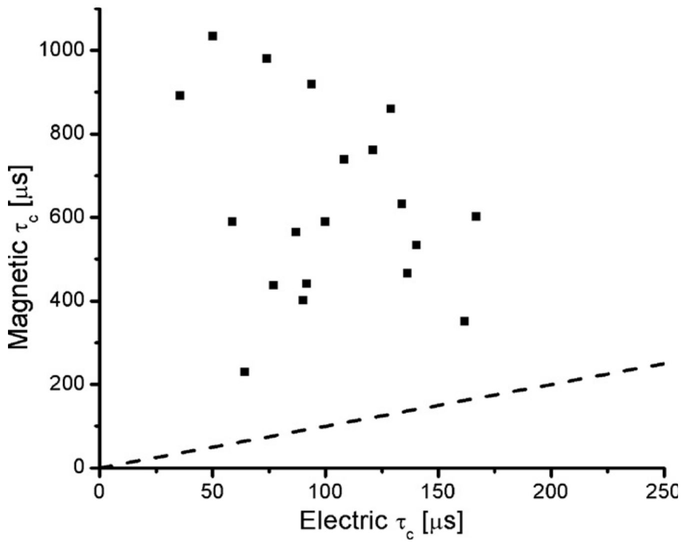

Figure 6. Scatter-plot comparing each electric stimulation τ_c to their corresponding magnetic stimulation τ_c for each single subject. The dashed line indicates the value where the electric τ_c is equivalent to the magnetic τ_c.

difference between the mean electric and magnetic chronaxie time, including all outliers, is still highly significant ($P < 0.001$).

Discussion

In the experiment described here, PNS chronaxie times were measured under conditions of both magnetic and electric field exposure for a paired subject group. The motivation for this

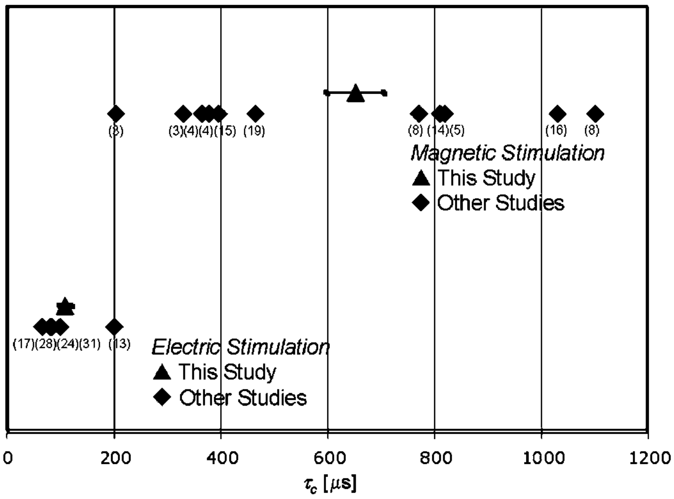

Figure 7. Dot diagram comparing the mean electric and magnetic τ_c calculated in this study to chronaxie times determined in other studies for both electric and magnetic stimulation. The triangle indicates the mean τ_c measured in our study. The diamonds indicate τ_c's determined in other published papers. The solid bar indicates the value of ± 1 standard error in the estimation of the mean τ_c from this study. Numbers below the diamonds indicate the reference for each published τ_c (as listed in order throughout the references).

comparison was to test the hypothesis that PNS parameters measured in electric field exposure experiments could be directly applied to PNS in MRI gradient coils. A localized magnetic field produced by a compact coil was used in an attempt to match as closely as possible the exposure conditions for both the electric and magnetic fields. The preliminary finding in this study is that the chronaxie times measured under the two exposure conditions are significantly different.

The electric field chronaxie values obtained in this study compare well with literature values (Reilly 1998, Holsheimer *et al* 2000, Rollman 1975, Sigel 1953, Hahn 1958), which range from 66 to 200 μs, as shown in figure 7. The values shown in the figure are from a variety of different experimental conditions and relate to different locations of stimulation. All of these studies stimulated the peripheral nerves, with the exception of Holsheimer *et al* (2000), which stimulated the central nervous system of subjects with Parkinson's disease or essential tremor. It is therefore possible that the chronaxie time measured in that study may be lower than those for normal subjects, due to the affects of motor disease (Ritchie and Smith 1944). For the peripheral nerve studies, stimulation electrodes were placed on the distal, anterior forearm, as in the present study, with the exception of Sigel (1953), which placed electrodes on the proximal, anterior forearm, and Hahn (1958), which placed the electrodes on the anterior hand and digit II. Both Holsheimer *et al* (2000) and Sigel (1953) measured individual thresholds by adjusting the applied voltage, whereas others controlled the stimulator current. The mean strength–duration time constant of Reilly (1998) is of particular importance to MRI, as it was the value used as the basis of international standards for many years (Athey 1992). The strength–duration time constant is converted to the chronaxie time used in this study by multiplying by ln2 (Panizza *et al* 1992). The Reilly strength–duration time constant of 120 μs is therefore equivalent to a chronaxie time of $\ln 2 \times 120\ \mu\text{s} = 83\ \mu\text{s}$, consistent with the values reported here.

The magnetic field PNS threshold chronaxie times measured in this study also compare well with literature values (Irnich and Schmitt 1992, Chronik and Rutt 2001b, Bourland *et al* 1996, 2001, Budinger *et al* 1991, Ham *et al* 1997, Hoffman *et al* 2000, Havel *et al* 1997) which range from 203 μs to 1100 μs. Figure 7 shows these values plotted together with the mean value of 651 μs obtained in this study. All of these studies (with the exception of Havel *et al* (1997) and Bourland *et al* (1996)) studied head-only or whole-body gradient coil systems. Havel *et al* (1997) and Bourland *et al* (1996) measured magnetic stimulation thresholds using a solenoid coil encircling the forearm, which is more similar to the exposure criteria used here, but not identical. Not all studies utilized a trapezoidal waveform for the magnetic stimulation. Irnich and Schmitt (1992), Budinger *et al* (1991) and Hoffman *et al* (2000) all used a sinusoidal waveform in their gradient coils. It must also be noted that Irnich and Schmitt (1992), Ham *et al* (1997), Budinger *et al* (1991) and Hoffman *et al* (2000) all employed a low number of subjects ($N < 5$ in all cases). These factors may explain the relatively large range of magnetic chronaxie times in the literature. However, it should also be noted that the literature magnetic chronaxie values are all significantly larger than the electric field chronaxie values, consistent with the findings reported here.

In the present study, it was observed across all subjects that electric and magnetic stimulation produced different sensations. For electric stimulation, sensation was typically described as localized directly below the electrodes on the surface of the skin. For magnetic stimulation, sensation was typically described as distributed throughout the palm and digits of the hand. In particular, most subjects reported sensations in either the medial or lateral digits. These observations suggest that electrical stimulation may preferentially activate cutaneous afferent nerve fibers whereas magnetic stimulation may preferentially activate deeper nerves, such as the ulnar or median nerve. Lotz *et al* (1989) reported that with electric stimulation, current flow between the anode and cathode depolarizes the fiber membrane at the cathode, and in order to activate deeper structures, a higher current density is required. It is entirely possible that the observed differences in chronaxie time are due to excitation of different groups of nerves, and in particular, it is possible that the changing magnetic fields preferentially excite motor nerves.

Other studies have compared the activation of sensory and motor fibers using electric and magnetic stimulation (Panizza *et al* 1992, Lotz *et al* 1989, Veale *et al* 1973). Lotz *et al* (1989) demonstrated through stimulation of nerve and muscle tissue that magnetic activation of intramuscular nerve fibers in the arm and leg occurs at a lower threshold than for electric stimulation. Also, sensory fibers were shown to have a lower threshold for electric stimulation. Electric stimulation of the wrist by Veale *et al* (1973) determined that when short pulses are used (less than 200 μs), motor fibers are more readily excitable, whereas for long pulse durations (greater than 1000 μs), sensory fibers are more prone to depolarization. A related observation by Panizza *et al* (1992) is that electric stimulation preferentially activates sensory fibers compared to motor fibers for long pulse durations, and the inverse for short pulse durations. They also report that for magnetic stimulation, the motor fiber threshold was lower than that for sensory fibers.

In this study, threshold was simply defined as any sensation or muscular contraction invoked by the stimulator, as was the case in work by others (Schaefer *et al* 2000, Cohen *et al* 1990, Irnich and Schmitt 1992, Chronik and Rutt 2001b, Bourland *et al* 1996, 2001, Budinger *et al* 1991, Ham *et al* 1997, Havel *et al* 1997). Therefore, the measured threshold curves reported here are probably combinations of sensory and motor fiber thresholds. Since there is a different threshold for motor and sensory fibers, the chronaxie time calculated from this strength–duration curve may be distorted by this effect depending on the population of nerves being stimulated. In studies to extend this work, electromyography is being implemented to distinguish between sensory and motor fibers and a separate chronaxie time is calculated for each fiber population. Similarly, Bourland *et al* (1996) have measured a lower chronaxie time for motor fibers as compared to sensory fibers using sinusoidal dB/dt pulses as stimuli.

The smaller chronaxie time for electric stimulation may be attributed to the effect of the electrode contact area. Pfeiffer (1968) demonstrated that if the electrode area is increased, the threshold current also increases. In relation to chronaxie time, he also showed that for larger electrode sizes, there is a shorter chronaxie time. Reilly (1998) has also documented this effect. His studies showed that for the forearm, the threshold is larger for a larger electrode area.

Geddes (2004) has noted that chronaxie values should be determined from a strength–duration curve measured by a constant current stimulator. In comparison with a constant voltage stimulator, which this study has utilized, the current waveform will not be the same as the voltage waveform due to the relationship of the electrode–subject impedance. However, other studies (Holsheimer *et al* 2000, Sigel 1953) have employed the use of a constant voltage stimulator and reported similar chronaxie times to studies that utilized a constant current stimulator (Reilly 1998, Rollman 1975, Hahn 1958). The induced electric field from a changing magnetic field results in an effectively constant voltage stimulus (assuming that the magnetic field is being switched at a constant rate during a given pulse, as was this case in this study); therefore, the electric and magnetic field exposure conditions used here were consistent in the sense that both were constant voltage stimuli. For these reasons, we suggest that the type of electric stimulator (constant voltage versus constant current) was not the source of the differences reported here; however, it seems clear that this effect should be investigated further in future studies.

In conclusion, this work indicates, for reasons that are yet to be fully explained, that the electric stimulation chronaxie times are significantly shorter than the effective magnetic stimulation chronaxie times. We are not suggesting that this observation casts any doubt on the basic mechanism of magnetically induced PNS, namely, that the changing magnetic fields induce electric fields that result in stimulation of the peripheral nerves. Rather, we believe that the primary consequence of these results is the realization that significant adjustments may need to be made to nerve parameters taken from the electric field stimulation literature prior to applying them directly to magnetic stimulation, as in the case of gradient coil operation in MRI. Because there is such strong motivation to increase gradient system performance for a variety of MRI applications, it is critical to understand gradient-induced PNS thresholds in detail. If there are indeed systematic differences between nerve chronaxie times as measured with electric versus magnetic fields, as indicated by this study, then these must be taken into account in setting gradient system operational guidelines. As such, if the chronaxie for magnetic stimulation can be consistently measured to be larger than the electric chronaxie, then stronger gradients could be used in MRI operation at a given τ value than would have been expected using data extrapolated from electrical stimulation. Further research in this area will likely yield more information regarding the underlying source and scope of these differences, and these studies are ongoing.

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Appendix A

The following is a derivation of the magnetic stimulation threshold curve (equation (2)) as a function of magnetic pulse sequence parameters and the electric field stimulation threshold (equation (1)).

Following Irnich and Schmitt (1992), the fundamental law of electrostimulation is used as the starting point, where the time average magnitude of the electric field ($\bar{E}_{\text{stim}}$) required to cause stimulation of a peripheral nerve is given by the following hyperbolic relationship:

$$\bar{E}_{\text{stim}} \equiv \frac{1}{\tau} \cdot \int_0^\tau E(t)\,\mathrm{d}t \geqslant E_r \cdot (1 + \tau_c/\tau), \tag{A.1}$$

where $E(t)$ is the magnitude of the applied electric field as a function of time during the electric field pulse and τ is the duration of the electric field pulse. Here, E_r is known as the electric field rheobase and is defined as the minimum electric field required for stimulation of a nerve under conditions of constant exposure, and chronaxie time, τ_c, is the electric field pulse duration for which the stimulation threshold is twice the rheobase value.

The electric field can be expressed as a combination of the gradient of the scalar potential due to a charge distribution ($\vec{\nabla}\Phi$), and the time derivative of the vector potential ($\vec{A}$) due to a current distribution:

$$\vec{E}(\vec{r}, t) = -\vec{\nabla}\Phi - \frac{\partial \vec{A}(\vec{r}, t)}{\partial t}. \tag{A.2}$$

In the context of the present application, the vector potential would be caused by the current distribution of the magnetic coil, and the scalar potential would arise due to the charge distribution formed within the tissue as a result of its exposure to the external vector potential. If the time rate of change of the applied magnetic field is small enough for the quasi-static approximation to be satisfied (Roth *et al* 1991), then the accumulation of charge within the tissue will be in phase with and proportional to the applied vector potential. This approximation is generally a good one for human tissues exposed to magnetic fields changing at frequencies less than 100 kHz, as is the typically the case for gradient coil operation in MRI. The total induced electric field can then be expressed as:

$$\vec{E}(\vec{r}, t) = -\vec{A}_o(\vec{r}) \cdot \frac{\mathrm{d}I}{\mathrm{d}t} \tag{A.3}$$

where $I(t)$ is the time varying current through the magnet coils. $\vec{A}_o$ is a function of position only and represents the combination of the vector and scalar potential contributions to the induced electric field (normalization per unit Ampere).

The magnetic field produced by the coil is proportional to the current through the coil:

$$B(t) = \eta \cdot I(t) \tag{A.4}$$

where η is the magnetic field efficiency (T/A) of the coil at the location of interest. The field efficiency is constant, and therefore equations (A.3) and (A.4) can be combined to obtain:

$$E(t) = \frac{A_o}{\eta} \cdot \frac{\mathrm{d}B}{\mathrm{d}t} \tag{A.5}$$

where $E(t)$ is now taken to be the magnitude of the total induced electric field.

Equation (A.5) can now be inserted within the threshold relation (equation (A.1)) to obtain the following:

$$\frac{A_o}{\eta} \cdot \int_0^{\tau} \frac{\mathrm{d}B}{\mathrm{d}t}\,\mathrm{d}t \geqslant E_r \cdot (\tau + \tau_c) \tag{A.6}$$

$$\Delta B_{\mathrm{stim}}(\tau) \geqslant \left(\frac{\eta}{A_o} E_r\right) \cdot \tau + \left(\frac{\eta}{A_o} E_r \cdot \tau_c\right) \tag{A.7}$$

where $\Delta B_{\mathrm{stim}}(\tau)$ is the total change in the magnetic field over a time τ required to cause stimulation. The first bracketed factor in (A.7) has units of T/s, while the second has units of T; therefore, the magnetic field threshold equation can be parameterized more simply as:

$$\Delta B_{\mathrm{stim}} \geqslant \left(\frac{\mathrm{d}B}{\mathrm{d}t}\right)_{\mathrm{min}} \cdot \tau + \Delta B_{\mathrm{min}}. \tag{A.8}$$

The definition of the quantities $(\mathrm{d}B/\mathrm{d}t)_{\mathrm{min}}$ and ΔB_{min} are clear from the comparison of (A.7) and (A.8). This model (including respective variants) has been used extensively throughout the literature (Schaefer *et al* 2000, Irnich and Schmitt 1992, Bourland *et al* 2001, Chronik and Rutt 2001a, Chronik and Ramachandran 2003, Reilly 1989, Den Boer *et al* 2002).

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