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Detection of Peripheral Nerve and Skeletal Muscle Action Currents using Magnetic Resonance Imaging

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Abstract

Many researchers have attempted to detect neural currents directly using magnetic resonance imaging (MRI). The action currents of a peripheral nerve or skeletal muscle create their own magnetic field that can cause the phase of the spins to change. Our goal in this paper is to use the measured magnetic field of a nerve or muscle to estimate the resulting phase shift in the magnetic resonance signal. We examine four cases: the squid giant axon, the frog sciatic nerve, the human median nerve, and the rat EDL muscle. In each case, the phase shift is much less than one tenth of one degree, and will be very difficult to measure with current technology.

Keywords

MRI; action currents; phase shift; nerve; muscle

INTRODUCTION

Many researchers have attempted to detect neural currents directly using magnetic resonance imaging (MRI) (2,5,10,12,15). The action currents of a nerve or muscle create their own magnetic field (18,24) that can act like a gradient field during magnetic resonance imaging, causing the frequency or phase of the nuclear spins to change because of the presence of the action current. However, this magnetic field is very small, and it is not clear if this effect will be measurable. Our goal in this paper is to use the measured magnetic field of a peripheral nerve or skeletal muscle to estimate the resulting phase shift in the magnetic resonance signal.

Magnetic measurement of action currents using magnetic resonance would be important because it would allow true functional imaging of action currents using all the power and resolution of MRI. Researchers have developed functional MRI to detect brain activity, which measures the blood oxygenation level-dependent (BOLD) signal (14). However, BOLD is an indirect measurement of perfusion rather than a direct detection of neural activity. Ideally, measurement of the magnetic field of action currents would provide a signal that better follows the spatial and temporal distribution of neural activity. Biomagnetic measurements using magnetometers outside the body have been used to measure neural activity directly (6,9,16). However, MRI measurements would detect the magnetic field inside the body, eliminating the ill-posed and difficult inverse problem that normally plagues biomagnetic studies. For this reason, magnetic resonance detection of action currents has generated much interest in the past few years.

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Previous studies by the MRI research community have attempted to calculate the magnetic field associated with action currents from first principles (4,15). However, a large body of research exists in the biomagnetic literature in which magnetic fields of nerves, muscles, and even single axons were calculated numerically (19,26) or directly measured using ferrite-core, wire-wound toroids (7,8,18,21,22,23,24,25). Our goal in this paper is to use some of these experimental results to estimate the MRI signal caused by action currents. We focus primarily on action potentials of the peripheral nervous system. Electrical activity in the brain, often of dendritic origin, may lead to different results, and we briefly address that in the discussion.

METHODS

Action currents in nerves and muscles have been directly measured using toroidal pickup probes by us and our former colleagues (8,22,23,25). From these measurements of the current, I , and the radius of the fiber, r , we can calculate the magnetic field created by this current at the surface of the fiber using the Ampere's law,

$$B = \frac{\mu_0 I}{2\pi r}, \quad (1)$$

where μ_0 is the magnetic permeability of free space.

Even though this expression represents an approximation for evaluating the magnetic field created by a nerve axon or a muscle fiber in the body, it is a reasonable approximation for distances very close to the fiber (26). However, the fall-off of the magnetic field is proportional to $1/r$ only at the surface of the nerve, and is much faster thereafter. In the magnetic resonance signal, this magnetic field will induce a phase shift, ϕ , of

$$\phi = \gamma B \Delta t, \quad (2)$$

where γ is the gyromagnetic ratio of a proton ($2.7 \times 10^8 \text{ s}^{-1} \text{ T}^{-1}$), B is the strength of the magnetic field created by the nerve or the muscle, and Δt is the duration of the rising phase of the action potential. This phase shift is an invaluable tool to investigate whether a noticeable event occurs in the MR signal due to action currents in nerves and muscles.

RESULTS

We have investigated the phase shifts due to four different measured action currents, from the squid giant axon, the frog sciatic nerve, the human median nerve, and the rat EDL muscle.

1) Squid Giant Axon

The squid axon is historically one of the most important bioelectric systems studied (11), and is one of the largest single axons known. Wikswo and van Egeraat (23) measured the action current associated with a propagating action potential along a squid giant axon, and obtained $I = 6 \mu \text{ A}$. Hodgkin and Huxley (11) reported that the radius of the squid giant axon, r , was about 0.5 mm. Thus, the calculated value of B at the surface of the axon, from Eq. 1, is 2.4 nT. The rise time is approximately 0.4 ms, so the induced phase shift, from Eq. 2, is about 0.00026 radians, or 0.015° .

Let us also compute the average of this magnetic field over one voxel located adjacent to the axon. This can be done by integrating the magnetic field given in Eq. (1) over the surface of a voxel and dividing it by the area of the voxel. The computed average magnetic field over a 1 mm voxel is 1.32 nT, which is, as expected, smaller than the magnetic field at the surface of

the axon. The average magnetic fields of the next two adjacent voxels along the radial direction are 0.61 nT and 0.40 nT, respectively. Therefore, these average magnetic fields offer even smaller phase shifts than that present at the surface of the axon.

The spatial extent of the upstroke of the action potential is 8.8 mm since the propagation speed of the signal is 22 m/s (23). Therefore it will cover about 9 adjacent voxels with 1 mm dimension. Averaging over voxels along the direction parallel to the axon could improve the signal to noise ratio without blurring or attenuating the phase shift, whereas averaging perpendicular to the axon significantly reduces the observed phase shift.

2) Frog Sciatic Nerve

The frog sciatic nerve consists of thousands of individual small axons. Wijesinghe and colleagues (22) measured the action current when a strong stimulus excites most of these axons, and found $I = 0.2 \mu\text{A}$ and $r = 0.75 \text{ mm}$. Thus, B is 0.05 nT. The rise time is 1 ms, so the induced phase shift is about 0.0007° .

3) Human Median Nerve

The first intraoperative recording of the action current of the human median nerve bundle was reported by Wikswo et al. (25) using an openable, toroidal pickup coil. They found the current to be $I = 0.35 \mu\text{A}$. The radius of the median nerve bundle is $r = 2 \text{ mm}$. Therefore, the corresponding magnetic field at the surface of the bundle is 0.035 nT. The rise time is about 0.75 ms. Therefore, the calculated phase shift is about 0.0004° .

4) Rat Extensor Digitorum Longus (EDL) Muscle

Like a nerve, a muscle consists of many individual muscle fibers. Gielen et al. (8) measured $I = 3 \mu\text{A}$ in a rat EDL muscle. However, the radius of this muscle, r , is large compared with the above mentioned nerves and is about 1.5 mm. Thus, $B = 0.4 \text{ nT}$ for the EDL muscle. The rise time is 1.2 ms and, therefore, the phase shift is 0.007° .

At least for the above systems, the phase shifts are very small; less than one hundredth of a degree except for the squid giant axon which is slightly more than one hundredth of a degree.

We can also look at the size of the phase shifts from another point of view. In NMR spectroscopy, one often measures the chemical shift, which specifies the fractional change in the resonant frequency for different chemical species and is typically on the order of a few parts per million. In our case, the static magnetic field during MRI is about 1 T and the magnetic field of the nerve or muscle is about 1 nT, implying a fractional change of magnetic field (analogous to a chemical shift) of about one part per billion. Thus, we expect a frequency resolution of about one thousand times that of NMR spectroscopy would be required to detect the magnetic signal of the nerve or muscle.

Another way to look at this is to consider the MRI signal caused by magnetic susceptibility inhomogeneities. Callaghan (3) has shown that the fractional change in magnetic field caused by a magnetic susceptibility inhomogeneity is on the order of the susceptibility difference between tissues. The magnetic susceptibility of many tissues is on the order of 10^{-5} , and differences between tissues are typically on the order of 10^{-6} . Thus, like the chemical shift, magnetic susceptibility signals correspond to fractional magnetic field changes on the order of parts per million. Biomagnetic signals from nerve and muscle are on the order of parts per billion, or one thousand times smaller than susceptibility effects in typical clinical MRI systems. These troublesome susceptibility signals are readily detected in an MRI scanner.

Let us consider yet another method to assess the size of these effects. The BOLD effect is related to the changes in physiological conditions and appears as a part of the time constant T_2^* . In general

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{\gamma B}{2} \quad (3)$$

T_2 is typically on the order of 50 ms. Therefore, $\frac{1}{T_2}$ is about 20 s^{-1} . For nerve bundles B is about 1 nT and hence $\frac{\gamma B}{2}$ is about 0.135 s^{-1} . Thus, the nerve magnetic field changes T_2^* by less than one percent.

DISCUSSION

We found that in four common bioelectric systems, the phase shift induced during MRI is small (typically less than one hundredth of a degree), and would probably not be measurable with current technology. Therefore, we are not optimistic about the future of such techniques. In fact, we believe our results above overestimate the MRI signal for the following reasons. 1) The magnetic field of an action potential consists of a biphasic signal with both depolarization and repolarization signals. The repolarization current lasts somewhat longer than the depolarization current, but is also weaker, so the integrated phases from depolarization and repolarization have the same magnitude but opposite sign. Thus, the net signal of the action current is nearly zero, as the phase shifts of depolarization and repolarization cancel. The entire action potential is over in just a few milliseconds, which is a short time compared to most MRI imaging pulse sequences. Thus, action potentials will be more difficult to detect than predicted above, unless very brief, carefully timed pulse sequences are developed. 2) In the case of the nerve, the action potentials in different axons propagate at different speeds, so that the compound action potential results from the summation of many single axon signals (22). Therefore, the measured signal will decrease as the action potentials propagate and become less well synchronized. 3) We calculate the magnetic field just outside a nerve or muscle fiber, where it is largest. In general, the field will fall off with distance outside the fiber (Eq. 1). We estimated that averaging over a voxel should result in a reduction of the phase shift in voxels near the axon, and very small phase shifts in voxels farther from the axon. 4) In most cases, the entire nerve or muscle will not be simultaneously active. Whereas for an isolated frog sciatic nerve it is fairly easy to stimulate most or all of the axons using supramaximal stimulation, in an experiment on a median nerve of a conscious human only a small fraction of the axons in a nerve will be active. We can confirm this fact by comparing the data presented in this paper for the frog sciatic nerve bundle and the human median nerve. Even though the radius of the human median nerve is much larger than that of sciatic nerve, the current recorded in the human median nerve is much smaller than that of the frog sciatic nerve. This proves that the active fibers in the human median nerve bundle are fewer than that in the maximally stimulated frog sciatic nerve bundle. Supramaximal stimulation of the median nerve in a conscious human would likely lead to violent muscle contractions and pain. Therefore, the probability of detecting the magnetic field of a human peripheral nerve in any clinical application may be even less than that suggested by our analysis of a frog sciatic nerve. 5) The value of the magnetic field may also vary depending upon which axons or sub-bundles are being stimulated in a human nerve. However, therefore, this may or may not overestimate the MRI signals.

Truong and Song (20) recently introduced another method called “Lorentz Effect Imaging” for detection of action currents using MRI. This method is based on the principle that when a current is placed in a magnetic field, there exists a force--the Lorentz force--on the current.

This Lorentz force will cause a current-carrying nerve to shift from its original position in the body. If there simultaneously exists a magnetic field gradient during the MRI, this movement of the axon causes the spins to diphase, resulting in an artifact in the magnetic resonance signal. Roth and Bassar (17) recently investigated this effect using a mathematical model and found that the Lorentz displacement was too small to be detected using MRI techniques. In fact, they concluded that the Lorentz force effect will be even smaller than the effect examined in this paper.

In this paper, our analysis focused only on peripheral nerves and skeletal muscle. Other systems that might give larger results are the brain and the heart. In the heart, a very large area of cardiac tissue is simultaneously active, and this may provide a good starting place to search for action currents recorded using MRI (although motion artifacts will certainly be a problem). If large regions of the brain are simultaneously active, the magnetic field around these active regions may be larger than we estimate here. Moreover, if the signal is caused by dendritic currents, it may not have the rapid repolarization currents to cancel the depolarization signal. These two systems need to be examined in more detail. In particular, analysis of the brain is important because of the great interest in functional studies of cognition. If we consider one column in the brain, having an area of roughly one square millimeter, the magnetic field might be similar to that found for the squid axon. In this case, dendritic currents would likely be driven by transmembrane potentials on the order of 10 mV rather than 100 mV in an action potential. However, the voltage drop may occur over a smaller extent, say 1 mm rather than nearly 10 mm for the propagating action potential in the squid. The brain consists of many cells, such as glial cells, in addition to neurons, so it is unlikely that the cross sectional area of active tissue will approach that in a single giant axon. On the other hand, dendritic currents may last longer than an action potential, resulting in a greater phase shift for a given magnetic field. Although we have not analyzed this case quantitatively, these various factors seem to at least partially cancel, suggesting that the predicted phase shift from a single column in the brain may not be too different from the phase shift predicted for a giant axon, about a hundredth of a degree. Slow dendritic currents may not suffer from cancellation of depolarization and repolarization signals, but we did not even consider this effect in the estimations in the Results section. Thus, unless a large fraction of the brain was simultaneously active, neural phase shifts should be very small.

Our model of the magnetic field is simple, and parameters in different nerves may vary. A more detailed calculation of the magnetic field of a single axon has been described previously (26) which shows that far from the axon, the magnetic field calculation is quite complex, but near the axon the simple Ampere's law model we use in Eq. (1) is quite accurate. Perhaps in some systems the parameters could be different, leading to a larger signal. However, even if these parameters would somehow magnify the signal by a factor of ten, the phase shifts would still be only about a tenth of a degree.

Our estimates of the fractional change in magnetic field strength or frequency caused by action currents assumes that the magnetic resonance study is performed using a typical static magnetic field strength on the order of 1 T. However, action currents might be detected more easily using ultra-low field MRI systems (5,13). The ability of these systems to detect biomagnetic signals is yet to be explored on living tissues. Because the biomagnetic field is not proportional to the static magnetic field (as it would be for chemical shift or susceptibility effects), a lower static field means a larger fractional change in frequency caused by action currents. Thus, ultra-low field measurements may be one way to better detect action currents. Perhaps clever experiments where a large field is used to polarize the spins increasing the signal-to-noise ratio but is reduced during detection of the signal would be useful, if the field could be switched rapidly enough without causing other confounding effects.

In conclusion, we find that MRI measurements of action current in nerve and muscle are unlikely using current technology. Bandettini et al. (1) asked if detecting neural activity using MRI is "fantasy, possibility, or reality?" Our results suggest that, at least for peripheral nerves and skeletal muscle, "fantasy" may be closer than "reality". Nevertheless, researchers studying magnetic resonance imaging continue to develop ingenious and sometimes amazing new imaging methods, using either more sophisticated pulse sequences or data processing techniques. Hopefully our analysis in this paper will help clarify the challenges that need to be overcome in order to achieve true functional imaging of neural activity.

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