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Carbon Nano-Structured Neural Probes Show Promise for Magnetic Resonance Imaging Applications

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Abstract

Objective—Previous animal studies have demonstrated that carbon nanotube (CNT) electrodes provide several advantages of preferential cell growth and better signal-to-noise ratio when interfacing with brain neural tissue. This work explores another advantage of CNT electrodes, namely their MRI compatibility. MRI-compatible neural electrodes that do not produce image artifacts will allow simultaneous co-located functional MRI and neural signal recordings, which will help improve our understanding of the brain.

Approach—Prototype CNT electrodes on polyimide substrates are fabricated and tested *in vitro* and *in vivo* in rat brain at 9.4T. To understand the results of the *in vitro* and *in vivo* studies, a simulation model based on numerical computation of the magnetic field around a two-dimensional object in a tissue substrate is developed.

Main Results—The prototype electrodes are found to introduce negligible image artifacts in structural and functional imaging sequences *in vitro* and *in vivo*. Simulation results confirm that CNT prototype electrodes produce less magnetic field distortion than traditional metallic electrodes due to a combination of both superior material properties and geometry. By using CNT films, image artifacts can be nearly eliminated at magnetic fields of strength up to 9.4T. At the same time, the high surface area of a CNT film provides high charge transfer and enables neural local field potential (LFP) recordings with an equal or better signal-to-noise ratio (SNR) than traditional electrodes.

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Significance—CNT film electrodes can be used for simultaneous MRI and electrophysiology in animal models to investigate fundamental neuroscience questions and clinically relevant topics such as epilepsy.

Keywords

electrode; functional magnetic resonance imaging (fMRI); magnetic susceptibility; carbon nanotubes (CNTs)

3. Introduction

Measurement of neural signals is a topic of great current interest, as seen by recent advances in recording of neural electrical signals with high amplification [1] and measurement of dopamine in the brain [2] using voltammetry. This interest is motivated by the desire to utilize neural signal measurements in feedback for deep brain stimulation. Yet another motivation is to learn about brain function by studying brain region response to various visual, audio and other external stimuli. However, studying brain function would highly benefit from being able to simultaneously measure neural signals and measure non-invasive fMRI hemodynamic response at the same location in the brain [3]. Currently, it is not possible to measure co-located neural signals and fMRI BOLD signals in the brain. This is because the differences in magnetic susceptibility between neural recording electrodes and brain tissue produce severe image artifacts at the electrode location, eliminating the possibility of co-located study, especially in ultra-high magnetic field MRI systems [4,5].

If neural electrodes that produce little or no artifacts in fMRI images could be developed, then fMRI BOLD signals could be measured at the same location as the neural signals, enabling modeling and study of the coupling between neural signals and hemodynamic changes.

This paper focuses on the properties of carbon nanotube (CNT) electrodes and presents the finding that very low image artifacts are produced with these electrodes, even when used with very high (9.4T) magnetic field MRI systems. Because magnetic field distortions and subsequent image artifacts are more severe at higher field strengths, lack of image artifacts at 9.4T should apply to lower (clinically relevant) field strengths such as 1.5T, 3T, and 7T as well. However, these electrodes are intended for use in animal models in order to better understand brain function, and high field systems are commonly used for such animal studies for obtaining higher image resolution. The bio-compatibility of these electrodes for future human use is not considered in this paper, since the electrodes are not intended for human use.

CNT electrodes have garnered significant interest in the neural electrophysiology community for other reasons, namely the observation that preferential growth and proliferation of neural cells occur on CNT surfaces [6], and the observation that increased neural signaling [7] is found on CNT surfaces *in vitro* and *in vivo* [8]. Another advantage of CNT electrodes is their capacitive charge transfer mechanism. Neural electrodes may transfer charge by Faradaic or capacitive means, or a combination of the two mechanisms. Faradaic charge transfer involves redox reactions occurring at the electrode tissue interface,

and charge balancing is required to prevent irreversible reactions that cause electrode and tissue if the electrode is used for stimulation. Conversely, capacitive charge transfer is limited to ion motion in the electrochemical double layer, which is inherently safer and protects the electrode and tissue but limits the maximum charge transfer [9]. CNT electrodes are dominated by capacitive charge transfer mechanisms, and as such are suitable for creating safer stimulation electrodes [10]. Meanwhile, the high surface area of CNT electrodes can help to overcome some of the limitations of reduced charge transfer density of capacitive charge transfer mechanisms. Furthermore, other researchers have shown that nanostructured carbon film electrodes can potentially reduce eddy currents in electromagnetic fields. Since the nanotubes in the CNT film electrodes are randomly distributed, the eddy current flow is disturbed and weaker eddy currents are seen than metallic electrodes under the same magnetic fields [11]. Finally, CNT yarn electrodes have previously been studied in MRI and were found to produce significantly reduced artifacts compared to commercial platinum-iridium DBS electrodes [12,13]. However, such studies were performed at modest field strengths (3T) and did not show functional echo planar imaging (EPI) data around the CNT yarn electrodes.

The MRI image artifacts at an electrode location are caused by local magnetic field distortions due to a change in the volume magnetic susceptibility (denoted by χ) at the substrate-tissue interface [14]. Image artifacts highly compromise the MR-signals originating from locations nearby the implanted electrode, preventing the collection of co-located electrophysiology and fMRI data. These artifacts are particularly large in the case of electrodes with significant volume magnetic susceptibility differences from the surrounding brain tissue, for example with traditional neural electrodes made of tungsten or platinum. Further, functional imaging sequences utilizing the blood-oxygen-level dependent (BOLD) contrast are especially artifact prone due to their echo-planar readout and T_2^* weighting that makes them sensitive to changes in magnetic susceptibility.

We focus on the investigation of carbon nanomaterial conductors for artifact reduction in this paper through simulation, *in vitro* evaluation with phantom brain tissue, and *in vivo* experimentation with rat brain studies, to better understand the physics underlying the reduced artifacts observed around these electrodes. Further, we demonstrate to our knowledge, the first example of *functional* imaging data obtained around a carbon nanostructured neural probe. The studies in this paper show that the low artifacts and high neural signal quality obtained with CNT electrodes are the result of a simultaneous combination of three factors associated with CNTs, namely their magnetic susceptibility, film thickness and orientation, and their high surface area.

4. Methods

Electrode fabrication

The fabrication process for the MR-compatible electrode prototypes is outlined in Figure 1. A substrate polyimide film (PI, 3 mil; Kapton, HN) was prepared for deposition of nano-material film using layer-by-layer (LBL) nano-assembly methods similar to those performed by our group previously [15]. The film was soaked in 6 M NaOH for 20 minutes at 60°C, followed by 15 minutes soaking in a polyelectrolyte bath of poly(diallyldimethylammonium

chloride) (PDDA), then poly(sodium 4-styrene-sulfonate) (PSS), and again PDDA, each with 0.5 M NaCl.

Afterwards, a dispersion of CNT was prepared. 100 mg of multiwalled nanotubes with outer diameters from 20 to 40 nm was stirred in 40 mL of 3:1 H₂SO₄: HNO₃ for 90 minutes at 110°C. The dispersion was diluted to 200 mL, then repeatedly rinsed and filtered (0.22 µm pores) to a neutral pH. The nanotubes were flushed from the filter with deionized water, yielding approximately 50 mL of dispersion. The CNT dispersion was ultrasonically agitated for 60 minutes. The CNT nanomaterial was then drop cast onto the treated polymer substrate and allowed to dry. Electrostatic forces between the negatively charged nanomaterial and the positively charged polymer substrate improve film adhesion. Additional layers of nanomaterial may be drop cast to increase nanomaterial surface concentration. To create the electrodes, the desired geometry was cut from the substrate once dry. The electrodes were cut such that the connection end was located outside the field of view of the RF coil. Silver lead wire were attached to this distal end with conductive silver epoxy. The electrodes were insulated with polydimethylsiloxane (PDMS; Sylgard 184, Dow Corning, Midland, MI), leaving the recording tip exposed. The electrode tip is pictured in Figure 2. A, and the rough structure of drop cast CNT is depicted in the SEM image of Figure 2. B.

The thickness of the CNT film, composed of many layers of randomly oriented multi-walled carbon nanotubes, was measured with a surface profilometer and was found to range from 4 to 8.3 µm. The PDMS thickness was estimated to be on the order of several hundred µm by micrometer measurements at the base of the electrode.

In vitro study

In vitro MR artifact testing was performed with CNT electrodes in agar phantoms prior to *in vivo* study. Agar was prepared (2% wt.) in deionized water by heating and stirring on a hotplate. The liquid agar was poured around the CNT electrode in a cylindrical tube and allowed to cool to room temperature before imaging at 9.4T. Two additional phantoms were constructed for MRI comparison, containing a fine silver wire (254 µm diameter) and a single-channel 0.5 Mµ commercial tungsten microelectrode (127 µm diameter) respectively. The tungsten microelectrode is shown in Figure 3 C–D. The phantom preparation was the same as for the CNT electrodes.

In vivo study

A CNT electrode and a commercial linear probe array were implanted bilaterally into the somatosensory cortex of a male Sprague-Dawley rat under isoflurane anesthesia. The commercial probe array (NeuroNexus A4x8-5mm-200-200-413-A32, 15 µm thick) contained 4 shanks with 8 channels each (total 32 channels). The recording site area was 413 µm² of iridium and the average channel impedance was approximately 1 MΩ at 1 kHz. The electrode array is shown in Figure 3 A–B. Anesthesia was induced with 5% isoflurane, and then maintained between 1.5 and 3% isoflurane for the duration of the surgery and experiment. A (bilateral) craniotomy was performed over the primary somatosensory forelimb cortex (S1FL) in each hemisphere, and electrodes were implanted with a

stereotaxic system. Neural activity was simultaneously recorded from the probes under 1.6% isoflurane at 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, Salt Lake City, UT). An ex-vivo noise floor was recorded at the end of the experiment to compare the SNR of the probes. In order to compare the neural signal recording quality between the commercial probe and our CNT electrode, we selected a single channel from the commercial probe array that showed good performance and was positioned at approximately the same depth as the tip of the CNT probe. Noise filtering (60 Hz) was applied during post processing in MATLAB, and signals were low-pass filtered to isolate local field potentials (LFPs, < 500 Hz)

Additionally, MR-imaging was performed in anesthetized rats ($n = 3$) that were implanted with a single CNT electrode in the left somatosensory cortex. Again, anesthesia was induced with 5% isoflurane, and then maintained between 1.5 and 3% isoflurane for the duration of the surgery and experiment. The animal was intubated and catheterized via the femoral artery prior to being placed in an MR-compatible cradle, and secured with bite and ear bars. A small craniotomy was performed over the primary somatosensory forelimb cortex in the left hemisphere. A plastic anchor was attached to the contralateral skull for electrode stabilization. The electrode was inserted into the cortex using a stereotaxic system, and dental cement was applied to secure the electrode and close the craniotomy. The animal's body temperature was maintained at 37°C with a heated water pad. Artificial breathing controlled by a ventilation machine was adjusted to maintain normal blood gases. At the end of the study, a bolus of potassium chloride (KCl) was injected into a venous line to induce a heart attack. Imaging was performed on a 9.4T/31cm horizontal bore magnet with a VnmrJ console (Agilent, Santa Clara, CA) and a custom RF coil. Multi-slice gradient echo (GEMS) and fast spin echo (FSEMS) sequences were performed to acquire whole brain anatomical images in sagittal, axial, and coronal orientations with a resolution of 156.3 μm or 78.1 μm (FOV 40x40 mm, slice thickness 0.5 or 1 mm, 256x256 or 512x512 image matrix size). Functional imaging was acquired using T_2^* -weighted single shot echo planar imaging sensitive to the BOLD contrast (gradient echo EPI, TR 612 ms, TE 17 ms, FOV 40x40 mm, 64x64 voxels, slice thickness 1 mm, 1–3 slices).

MRI images were loaded into MATLAB with the AEDES toolbox. Network connectivity maps were calculated using a seed based correlation analysis [16] and overlaid on slice matched anatomical images with a threshold of $p < 0.05$ and correlation coefficient $|cc| > 0.5$.

Apparent electrode widths were measured from anatomical images using the average of 6 manual measurements in ImageJ (NIH, Bethesda, MD) and compared to 6 repeat measurements made at the same location in a digital optical microscope image (VHX-5000, Keyence, Itasca, IL).

All animal procedures were approved by the Institutional Animal Care and Use Committee at the University of Minnesota.

Simulation of field distortions

To investigate the effects of both the volume magnetic susceptibility and geometry of the electrodes during MRI, a 2D magnetic field simulator was implemented. Bhagwandien [17] and colleagues previously introduced such a solver to calculate magnetic field distortions corresponding to an object of interest, where the object is discretized and the discrete magnetic susceptibility of each node is defined. Our solver operates upon the same equations used by Bhagwandien et al., but we used a direct method to compute the solution rather than a convergent pseudo-time method. The solution details are provided in the appendix.

The accuracy of the solver was first checked by simulating a coaxial cylindrical cross-section and comparing the result with the analytical solution. The analytical solution is provided in [17]. We observed that the numerical solution agrees very well with the analytical solution. A moving average filter was applied to the numerical B-field solution along the circumference of the coaxial cylinder, to reduce the small oscillation errors found at the boundaries of susceptibility change.

The distortion of the B-field by an object was defined as the difference between the numerically calculated B-field and the analytical background B-field in the absence of the object, normalized by the background B-field, and reported in ppm. The root-mean-square (RMS) of the distorted B-field was used to compare the severity of field distortion across the field-of-view between simulations.

The RMS field distortions of the B-field by a foreign object as a function of susceptibility and geometry were simulated with 512 x 512 nodes and a field-of-view (FOV) of 819.2 μm x 819.2 μm (node spacing 1.6 μm). Several geometries were simulated including 127 μm and 254 μm diameter cylinders, and a rectangular probe 401.2 μm wide and consisting of three layers: 76.8 μm polyimide, 16 μm film of varying susceptibility, and 76.8 μm PDMS. The rectangular probe was simulated with the 401.2 μm edges perpendicular (orientation 1), and parallel (orientation 2) to the static magnetic field. These geometries were selected to correspond to physical electrode prototypes used in our tests.

In each case the principle axis of the object is oriented perpendicular to the static magnetic field, as is the case for implanted neural probes in our *in vivo* experiments. Due to the 2D nature of the simulation, the object is assumed infinitely long along its principle axis.

Additionally, we computed the RMS field distortions as a function of film thickness for the rectangular probe. The 401.2 μm wide probe parameters were used (the thickness of the polyimide and PDMS are the same as described above), but here the magnetic susceptibility of the film was set at -80 ppm, and the thickness was varied. Both orientations 1 and 2 were considered. To examine the influence of the polyimide and PDMS layers, we performed simulations without these layers, and with 401.2 μm thick PDMS (a very thick layer).

Simulated artifact visualization

To visualize susceptibility induced image artifacts in T_2^* -weighted images, we took the output from static magnetic field distortion simulations and grouped the nodes into voxels of realistic dimensions. Specifically, we simulated a tungsten wire with diameter 127 μm , a

silver wire with diameter 254 μm , and a rectangular probe with 282 μm width composed of three layers: 76.8 μm polyimide, 9 μm film of varying susceptibility, and 76.8 μm PDMS. For the film, susceptibility values from -20 ppm to -100 ppm were simulated in 20 ppm steps. A larger FOV was required to enable comparison of the simulation results and *in vitro* images, therefore we increased the FOV from $819.2 \times 819.2 \mu\text{m}$ to $2500 \times 2500 \mu\text{m}$, but 512×512 nodes were still used (node spacing 4.88 μm). The nodes were grouped into voxels of 16×16 nodes (that is 32×32 voxels in the FOV) and the magnetic field inhomogeneity (B_{in}) within each voxel was computed as the difference between the maximum and minimum value. The distortions were scaled for 9.4T (as the distortion simulations were normalized by static field strength) and superimposed on a frequency encoding gradient (G_f) of 14.678 G cm^{-1} (corresponding to *in vitro* experiment) prior to computing the voxel inhomogeneity. Afterwards T_{2*} was estimated for each voxel per Equation 11 [18]. The surrounding medium in our simulations is water, so we used the gyromagnetic ratio (γ) for hydrogen (42.58 MHz T^{-1}) in our computations. Notice that the term γB_{in} in Equation 11 becomes increasingly influential on T_{2*} at high field strengths. T_2 was assumed to be 40 ms for water at 9.4T [19] and was set at 500 μs for solids such as polyimide, PDMS, and CNT.

$$\frac{1}{T_{2*}} = \frac{1}{T_2} + \gamma \Delta B_{\text{in}} \quad (11)$$

In vitro data collection for comparison with simulated artifacts

Experimental *in vitro* imaging was performed to compare with simulated artifact visualization results. Phantoms were made by stirring and heating agar 2% wt. in de-ionized water. Three samples: a CNT on polyimide probe of width 282 μm , a 254 μm diameter silver wire, and a 127 μm diameter tungsten microelectrode, were each placed in their own tube and liquid agar was poured around them and allowed to set. A weak vacuum chamber was used to assist in removing bubbles from the agar solution with varying degrees of success.

Phantoms were imaged with an Agilent 9.4T 31-cm bore system using a proton (^1H) quadrature RF transmit-receive coil. Initially, phantoms were positioned in an MR-compatible cradle and inserted into the magnet bore. The coil was tuned and matched, and sagittal imaging was used to aid in positioning the sample at the magnet isocenter. After repositioning, the tune and match were again checked, and then 3D volume shimming was used to improve the homogeneity of the magnetic field. A T_{2*} -weighted gradient-echo sequence (flip-angle 30 degrees, $\text{TR} = 100 \text{ ms}$, $\text{TE} = 4.71 \text{ ms}$) was used due to its sensitivity to magnetic field inhomogeneities which can stem from changes in magnetic susceptibility. The image field-of-view was $40 \times 40 \text{ mm}$ with 512×512 voxels (in-plane resolution 78.1 μm), slice thickness was 1 mm, and 10 averages were used to improve SNR.

5. Results

In vitro study

CNT electrode prototypes were tested in agar phantoms to examine image artifacts at 9.4T prior to *in vivo* study. Example structural MR images of a CNT electrode in three

orientations are provided in Figure 4, along with a single profile view of the same electrode under an optical microscope. The MR images show that the electrode itself produces little to no artifact. Air bubbles that attached to the surface of the electrode during phantom preparation are responsible for the large dipole artifacts in the MR images. The lack of image artifacts around the electrode tip (cross-bar) prompted *in vivo* study of the electrode properties.

In vivo study

The utility of the prototype CNT neural probes was evaluated *in vivo* using a rat model. Local field potentials that were recorded simultaneously from a commercial linear probe array and a prototype CNT electrode in an anesthetized rat are presented in Figure 5A–B. As apparent from the figure, the prototype CNT electrode showed improved sensitivity to neural field potentials and a reduced noise level ex-vivo compared to the commercial neural probe, i.e. the CNT electrode demonstrated higher SNR in the LFP frequency range. The frequency spectrum of the recordings was also examined (Figure 5C) and confirmed improved sensitivity of the CNT probe compared to the commercial probe.

MR-imaging was performed in three separate anesthetized rats implanted with a single CNT electrode in the left somatosensory cortex, and images from one rat are presented in Figure 6. Both structural and functional images were taken. High resolution structural images are presented in the left column of Figure 6, the mean EPI signal is presented in the center column, and functional connectivity maps generated from the fMRI time course are presented in the right column. As illustrated by the *in vivo* images, the presence of the CNT electrode in the left hemisphere (image right) does not introduce significant artifacts in the structural nor functional imaging. The CNT neural probe is barely discernible in the FSEMS structural imaging, so we have indicated its location with red arrows. The mean EPI is provided to show that the presence of the electrode does not introduce a region of signal loss (artifact) around the electrode, which typically occurs around implanted metallic neural electrodes. Finally, a seed-based resting state connectivity map generated under 1.7% isoflurane anesthesia is presented to show that meaningful functional imaging data can be collected around the CNT neural electrode. Therefore, these CNT prototype neural probes could be used in simultaneous electrophysiology-fMRI studies, or even more broadly in MR applications, as they circumvent the image artifact problem that is present when using traditional metallic electrodes.

The apparent width of the CNT electrodes in optical and 9.4T MR structural images were measured for all three animal subjects to determine if MR artifacts were present around the implanted probes. The mean apparent width and standard deviation for each subject are presented in Figure 7. Except for the T_2^* -weighted image of electrode 2, the width of the electrode appears the same size or smaller in MR images than in optical microscope images, indicating little to no artifacts. For electrode 2, the large apparent width in T_2^* imaging is attributed to susceptibility change due to air bubbles present in the PDMS insulation. The T_2 -weighted image of the same electrode does not have a large apparent width, supporting the inference that the artifact was susceptibility induced by the presence of air bubbles. FSEMS and GEMS of the electrode implanted into the rat brain are presented in Figure 8 for

electrode 3. Again, the size of the electrode in both GEMS and FSEMS imaging in all three orientations indicates that the CNT probe does not cause image artifacts in the structural imaging.

Simulation of field distortions

The numerical solution validation is provided in Figure 9. A hollow coaxial cylinder of water in air with inner radius 80 μm and outer radius 120 μm was simulated with a grid of 512x512 and node spacing of 1.6 μm . The distortion of the B-field due to the presence of the coaxial cylinder is shown on the left side of Figure 9. Additionally, the analytical solution was computed and the difference between the numerical and analytical solution is provided on the right side of Figure 9. As seen in Figure 9, the results of the numerical solution are in good agreement with the analytical solution.

After validating the solution technique as shown in Figure 9, the distortions of the B-field by a foreign object as a function of susceptibility and geometry were simulated and the RMS values computed. See the methods section for specifics regarding the geometries simulated. The results are presented on the left side in Figure 10, and reveal that reducing the magnetic volume susceptibility difference between the object and the medium reduces the field distortion as expected. However, we also observe that the rectangular probe in orientation 2 (long edge of cross-section parallel to the static field) has reduced field distortions compared to the other three cases. Even strongly diamagnetic or paramagnetic films in probe orientation 2 might produce less field distortion than moderately diamagnetic and paramagnetic objects of other geometries.

RMS distortions as a function of film thickness are presented on the right side of Figure 10. As expected, the RMS field distortion increased with increasing film thickness. The strong diamagnetism of the -80 ppm film compared to PDMS and polyimide caused it to be principally responsible for the field distortions, as indicated by the close match between the results of the probe with polyimide and PDMS compared to results from simulations of the film without these polymer layers. As mentioned in the methods section, we also simulated the probe with a very thick PDMS layer. However, we found this influence to be negligible for the diamagnetic film with susceptibility difference of -70.95 ppm from the surrounding medium. The PDMS thickness would however affect the results for films with susceptibilities more closely matched to the surrounding medium, but then the overall field distortion would also be reduced.

Artifact visualization and comparison to in vitro data

Maps of simulated T_2^* -weighting were generated for artifact visualization and are shown below B-field distortions including the frequency encoding gradient in Figure 11. Rectangular probes with two polymer layers surrounding a film with susceptibility from -20 ppm to -100 ppm were simulated as well as a silver wire of diameter 254 μm and a tungsten wire with diameter 127 μm . For rectangular probes only the results from -20 and -40 ppm films are shown.

The top row of Figure 11 shows the distorted B-field around the various geometries simulated. The probe geometry is shown to scale in the upper right inset of each subfigure.

The frequency encoding gradient is superimposed as well, so that we can visualize the disturbances to the MR imaging system that are responsible for susceptibility induced artifacts. We observe essentially no disturbance to the system for the polymer probe with -20 ppm diamagnetic film, and a small disturbance for the case of the -40 ppm probe. Further, we see a much larger disturbance around the silver wire (corresponding to its size), and an intense disturbance around the tungsten wire due to its large susceptibility difference from the background medium (water).

From the signal strength term (middle row), we can make several observations. First, the tungsten wire (with largest susceptibility difference from water) produces a much larger artifact than its physical size. The size of the artifact from the silver wire is approximately the same size as the one from the tungsten wire, despite the silver wire have a diameter a factor of two larger. From this result it is clear that both susceptibility and geometry play a significant role in determining the artifact size. The orientation of the artifact between the tungsten and silver wires is flipped along the x-axis since tungsten is paramagnetic and silver is diamagnetic. For the rectangular probes, we might expect to see a uniform gray signal since disturbances to the B-field and frequency encoding gradient were small. However, T_2 for the solid polymer and diamagnetic films was set to be much shorter than that of water (corresponding to the real situation), resulting in a lack of signal from the probe location despite minimal distortions to the system. For the -20 ppm probe there is nearly no artifact surrounding the probe, and for the -40 ppm probe there is a small artifact.

Additionally, *in vitro* imaging was performed with samples corresponding to those simulated in Figure 11. An image slice near the middle of each object with few or no air bubbles in the surrounding agar was manually selected for comparison to simulation results. The selected slices are shown in the bottom row of Figure 11. We display a zoomed view of 32×32 voxels around each object to match our T_2^* simulations, which reveals excellent correspondence between the simulations and experimental images at 9.4T for both the tungsten and silver wires. The *in vitro* imaging of the CNT probe corresponds well to simulations of the rectangular probe with film susceptibility of -20 and -40 ppm. The simulation of film susceptibilities of -60 ppm, -80 ppm, and -100 ppm did not match the *in vitro* imaging and is not shown in Figure 11. Based on the correspondence between the tungsten and silver wires *in vitro* and in simulation, and the similar correspondence between the CNT probe *in vitro* and the simulations of the rectangular probes with susceptibility values -20 ppm and -40 ppm, we estimate that the CNT susceptibility value is near -30 ppm.

6. Discussion

In vivo experimentation in an anesthetized rat revealed that our prototype CNT neural electrodes can achieve higher SNR in the LFP frequency range than commercial electrodes as illustrated in Figure 5A–C. This SNR improvement is attributed to the high electrochemical surface area of the CNT electrode. Additionally, we found that both structural and functional MR images could be obtained around an implanted CNT electrode *in vivo* at a field strength of 9.4T with low artifacts. Similar to the results obtained with CNT yarn electrodes [12,13], we observed significant reduction in image artifacts in structural

MR images, further demonstrating the suitability of CNT as a conductor in MR-compatible neural electrodes. We have expanded on the previous work by demonstrating the reduced artifacts at much higher field strengths (9.4T vs. 3.0T) and by presenting functional EPI data that introduce the possibility of functional brain study with MRI around the CNT electrodes. The ability to obtain functional images around an implanted neural electrode with high SNR in neural LFPs is useful for improving our understanding of the brain, since simultaneous electrophysiology and functional hemodynamic/metabolic data could be combined to leverage the advantages of each modality. Specifically, the temporal resolution and high spatial specificity of electrophysiology, and the large spatial field-of-view of fMRI that can cover the whole brain.

The positive results obtained from *in vivo* experiments with the CNT prototype electrodes, particularly the successful collection of fMRI data around the probe, prompted us to investigate *why* this design avoided image artifacts. The initial hypothesis was that the CNTs must possess a volume magnetic susceptibility value near that of brain tissue, eliminating the susceptibility-induced image artifacts that are often seen around electrodes in T_2^* -weighted images. Indeed, the CNT susceptibility has been attributed as the primary mechanism of image artifact reduction in the past [12,13]. However, a review of the literature suggests that the magnetic properties of CNTs could vary widely depending on sample preparation and the length scale of interest. It should be noted that CNTs prepared by catalytic arc discharge from graphitic rods exhibit strong diamagnetic properties; on the other hand, CNTs grown with ferromagnetic catalysts contain impurities that produce ferromagnetic behavior [20,21]. We are interested in MR-applications so we will consider the former CNTs and not the latter. Nevertheless, converting the mass magnetic susceptibility values reported in the literature [22–26] to volume magnetic susceptibilities results in a broad range of possible values depending on how the CNT density is defined.

Converting the reported mass susceptibilities to volume susceptibilities with bulk-scale densities gives values on the order of –10 to –30 ppm, whereas using measures of true density (where only the volume of carbon without voids is considered) gives values on the order of –100 to –300 ppm. The first method is likely to be more appropriate for this application, since the length scales involved are cm-scale field of view dimensions, and indeed our simulations and *in vitro* imaging suggest that the susceptibility of our CNT films is around –30 ppm.

While a volume susceptibility of –10 to –30 ppm is a significant improvement over the corresponding values for paramagnetic electrodes such as tungsten or platinum, it is clear that CNT film electrodes are also not *perfectly* matched to brain tissue in terms of volume magnetic susceptibility. Are the low artifacts also a result of the differences in geometry between the CNT electrodes and the traditional platinum/tungsten electrodes? This question prompted us to further investigate the physics underlying the reduced image artifacts through computer simulation.

The results of our simulations indicate that both susceptibility and geometry play an important role in B-field distortions. Figure 11 highlights that field distortions can be reduced not only by providing a close match between volume magnetic susceptibility of the

probe to the tissue, but also by altering the probe geometry and orientation. Further, we could estimate T_2^* signal weighting maps from our simulations, allowing us to postulate an approximate value for the volume magnetic susceptibility of our CNT films. Considering both the results of the simulations and *in vitro* data, we conclude that our CNT electrodes benefited from geometry, specifically a thin film oriented in a manner that reduces field distortions, but that the magnetic volume susceptibility must still be relatively well matched with tissue to avoid artifacts. We estimate that the value is approximately -30 ppm, because both -20 ppm and -40 ppm simulated films produced T_2^* -weighted image simulations in excellent agreement with experimental data of prototype CNT electrodes, whereas simulations of -60 , -80 , and -100 ppm (not shown) were in poor agreement. Despite the different morphology of the CNTs between this study and that performed by Jiang and colleagues [12], where the susceptibility of CNT yarns was reported as -26 ppm, the susceptibility values are in good agreement.

7. Conclusions

The low artifacts observed when CNT electrodes are used for neural recordings in 9.4T MRI machines are due to a combination of better matched magnetic susceptibility, thin electrode films, and favorable electrode orientation. Based on the results of simulation and experimental *in vitro* imaging, we estimate the volume magnetic susceptibility of our CNT films to be approximately -30 ppm, which is in good agreement with Jiang [12] for CNT yarns. Comparing this value to 77.2 ppm for tungsten and 279 ppm for platinum, we find that the volume magnetic susceptibility of CNT is significantly closer to -9.05 ppm, the value for water (tissue) at physiological temperature [14]. However, there is still a significant difference between the value of CNT and water, and the simulations show that geometry and orientation also play a role in artifact reduction for these neural probes. Regarding lower film thickness, this would generally lead to poor conductivity, high impedance, and poor signal-to-noise ratio. However, the extremely high electrochemical surface area of the CNT electrode (depicted in Figure 2B) makes up for the low film thickness by reducing the impedance at the electrode-tissue interface and in fact provides a higher SNR for LFPs than the commercial probe array as was illustrated in Figure 5. Therefore, we conclude that rough CNT films are an excellent conductive material to employ in electrodes that are designed for use in MRI applications.

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Abbreviations

BOLD	Blood-oxygen-level dependent
CNT	Carbon nanotube
EPI	Echo planar imaging

fMRI	Functional magnetic resonance imaging
FOV	Field of view
FSEMS	Fast spin echo multiple slice
GEMS	Gradient echo multiple slice
LFPs	Local field potentials
PDMS	Polydimethylsiloxane
RMS	Root-mean-square
SEM	Scanning electron microscope
SNR	Signal-to-noise ratio
TE	Echo time
TR	Repetition time
B	Magnetic induction or magnetic flux density (T)
B_{in}	Voxel inhomogeneity (T)
G_f	Frequency encoding gradient (G cm ⁻¹)
H	Magnetic field strength (A m ⁻¹)
T₂	Ideal transverse magnetization relaxation time constant (ms)
T₂*	Imperfect transverse magnetization relaxation time constant (ms)
γ	Gyromagnetic ratio (42.58 MHz T ⁻¹ for proton)
μ₀	Magnetic permeability of free space (4π x 10 ⁻⁷ H m ⁻¹)
μ_r	Relative permeability (unitless)
χ	Magnetic volume susceptibility (unitless)
Φ	Magnetic scalar potential (A)
A	Matrix of weights for magnetic scalar potentials of interior nodes
B	Matrix of weights for magnetic scalar potentials of boundary nodes
I	Identity matrix
K	Right side of augmented matrix [A B] after reduction to reduced echelon form
Φ→	Vector of unknown magnetic scalar potentials of interior nodes
u→	Vector of defined magnetic scalar potentials at boundary nodes

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9. Appendix

Simulation of field distortions

The solution makes use of the magnetic scalar potential Φ , which is defined per Equation 1, where H is the magnetic field strength [17].

$$H = -\nabla\Phi \quad (1)$$

The problem is to calculate the unknown magnetic scalar potentials Φ at each node corresponding to the defined magnetic susceptibility distribution. Fortunately, an equation involving the magnetic susceptibility χ and magnetic scalar potential Φ exists. Specifically, for a magnetic permeability distribution μ_r (note that $\mu_r = \chi + 1$), the magnetic scalar potential Φ is constrained per Equation 2, that is the divergence of the product of the permeability and the gradient of the scalar potential is zero.

$$\nabla \cdot (\mu_r \nabla \Phi) = 0 \quad (2)$$

Our simulator calculates the magnetic scalar potential Φ corresponding to a defined magnetic volume susceptibility distribution χ , but a direct solution method is used rather than a convergent pseudo-time approach [17,27]. Expanding Equation 2 in two dimensions (x and z) results in Equation 3, where z is defined to be aligned with the applied static magnetic field and x is orthogonal to z .

$$\frac{\partial \mu_r}{\partial x} \frac{\partial \Phi}{\partial x} + \mu_r \frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial \mu_r}{\partial z} \frac{\partial \Phi}{\partial z} + \mu_r \frac{\partial^2 \Phi}{\partial z^2} = 0 \quad (3)$$

Equation 3 becomes a linear system when applied on a uniform grid and approximated by finite difference methods. See Figure A1 for a visualization of the grid. For a node with a scalar potential Φ_0 (node 5 in Figure A1), the first and second partial derivatives of Φ with respect to x and z can be approximated by the central difference method, leading to the form of Equation 4. The permeability of each node is defined to create the object of interest, so μ_r is known and the spatial partial derivatives of μ_r can be approximated by finite difference methods at each node on the grid. Therefore, μ_r and its approximate spatial derivatives are known for each node in the grid.

Figure A1.

Illustration of discretized magnetic scalar potential for a 3x3 grid around central node 5.

Gray nodes are not used in the central difference approximations on node 5.

$$\frac{\partial \mu_r}{\partial x} \left[\frac{\Phi_{0+\Delta x} - \Phi_{0-\Delta x}}{2\Delta x} \right] + \mu_r \left[\frac{\Phi_{0+\Delta x} + \Phi_{0-\Delta x} - 2\Phi_0}{\Delta x^2} \right] + \frac{\partial \mu_r}{\partial z} \left[\frac{\Phi_{0+\Delta z} - \Phi_{0-\Delta z}}{2\Delta z} \right] + \dots \mu_r \left[\frac{\Phi_{0+\Delta z} + \Phi_{0-\Delta z} - 2\Phi_0}{\Delta z^2} \right] \approx 0$$

(4)

Equation 4 can be easily rearranged into the discretized form of Equation 5, and used as a constraint on the magnetic scalar potential at each interior node, specifically a linear combination of the magnetic scalar potentials involving the central and four adjacent nodes. Strictly speaking, the partial spatial derivatives of μ_r in Equation 5 are approximated by discrete finite difference methods, but the continuous derivative notation is used so that the form of Equation 5 does not become unnecessarily complicated.

$$\Phi_0 \left[\frac{-2\mu_r}{\Delta x^2} + \frac{-2\mu_r}{\Delta z^2} \right] + \Phi_{0-\Delta z} \left[\frac{\mu_r}{\Delta z^2} - \frac{\frac{\partial \mu_r}{\partial z}}{2\Delta z} \right] + \Phi_{0+\Delta z} \left[\frac{\mu_r}{\Delta z^2} + \frac{\frac{\partial \mu_r}{\partial z}}{2\Delta z} \right] + \dots \Phi_{0-\Delta x} \left[\frac{\mu_r}{\Delta x^2} - \frac{\frac{\partial \mu_r}{\partial x}}{2\Delta x} \right] + \Phi_{0+\Delta x} \left[\frac{\mu_r}{\Delta x^2} + \frac{\frac{\partial \mu_r}{\partial x}}{2\Delta x} \right] \approx 0 \quad (5)$$

The bracketed scalar weights containing magnetic permeability and grid lengths in Equation 5 are computed for each node in the defined grid corresponding to the object of interest. Then, vectors Φ and u , and matrices A and B are defined to satisfy the constraints for all the interior nodes in the model as described below.

The vector Φ contains the unknown magnetic scalar potential at each interior node in the grid, and the vector u contains boundary conditions on the magnetic scalar potential at each boundary node. The boundary conditions are created by placing the boundary nodes far away from the object of interest and assuming the magnetic scalar potential at the boundary is unaffected by the presence of the object. The scalar potential at the boundary can be computed through integration of Equation 1 for a desired applied field H .

Matrices A and B are systematically defined so that Equation 5 is written for each interior node of unknown magnetic scalar potential. The number of rows in A and B are equal to the number of interior nodes in the grid, that is the number of unknown magnetic scalar potentials; A is a square matrix and the number of columns in B corresponds to the number of boundary nodes minus four, as the corners of the boundaries are not used by the central difference approximations on any interior nodes. The bracketed scalar weights for each interior node are assigned to the row corresponding to that node and the appropriate column in A or B such that the weights for each node are multiplied by the appropriate scalar potential in either Φ or u . The result is a system of linear equations containing Equation 5 for every interior node in the grid. The system is represented in Equation 6 as the sum of two matrix-vector products.

$$\mathbf{A}\vec{\Phi} + \mathbf{B}\vec{u} = \vec{0} \quad (6)$$

To reasonably discretize an object of arbitrary curvatures in a large enough field-of-view such that the boundary magnetic scalar potentials are unaffected by the object often requires

several hundred nodes in each direction. In such cases, A and B are sparse matrices, e.g. for a grid of 512x512 nodes the number of columns in A and rows in A and B is 260,100, and the number of columns in B is 2,040; but the number of nonzero entries in each row of an augmented matrix [A|B] is only five, corresponding to the five magnetic scalar potentials in Equation 5. Rather than solve Equation 6 for the unknown magnetic scalar potentials in Φ by inversion of the sparse matrix A, the system is rewritten in the form of Equation 7.

$$[\mathbf{A} \mid \mathbf{B}] \begin{bmatrix} \vec{\Phi} \\ \vec{u} \end{bmatrix} = \vec{0} \quad (7)$$

The solution is found by numerically computing the reduced row echelon form of the augmented matrix [A|B] which by definition has the form of the matrix in Equation 8, where $\mathbf{I}$ is the identity matrix the size of A.

$$[\mathbf{I} \mid \mathbf{K}] \begin{bmatrix} \vec{\Phi} \\ \vec{u} \end{bmatrix} = \vec{0} \quad (8)$$

Finally, the unknown magnetic scalar potentials can be calculated per Equation 9.

$$\vec{\Phi} = -\mathbf{K}\vec{u} \quad (9)$$

The magnetic induction or magnetic flux density B is calculated from the computed magnetic scalar potentials with finite difference approximations of Equation 10, which only applies for non-ferrous objects such that B and H are linearly related.

$$\mathbf{B} = \mu_o \mu_r \mathbf{H} = \mu_o \mu_r (-\nabla \Phi) \quad (10)$$

Through the approach described in Equations 1–10, we have computed the magnetic flux density, or B-field, around an object of arbitrary volume magnetic susceptibility distribution in an applied magnetic field of strength H.

Figure 1.

Fabrication flowchart. (A) The polymer substrate is prepared for electrostatic adhesion of nano-structured carbon electrodes using a layer-by-layer surface treatment method. (B) CNT dispersion is prepared with acid treatment and ultrasonic agitation. (C) The dispersion is drop cast on the polymer substrate, and (D) allowed to dry into a thin film inside the bounded area. (E) The electrode is cut out and (F) a wire and pin are attached prior to insulation with PDMS. (G) Photograph of prototype CNT electrode.

Figure 2.

Electrode tip and CNT structure. (A) Zoomed view of electrode tip showing exposed CNT recording surface. (B) Example image of the rough structure of drop cast CNT on a polymer substrate.

Figure 3.

Commercial microelectrodes used in the study. (A) Commercial linear probe array and (B) zoomed view of recording shanks. Shank length 5 mm and shank spacing 200 μm . The commercial linear array was used to compare neural signal recording quality against the CNT electrode but was not MR-compatible. (C) Commercial tungsten microelectrode and (D) zoomed view of tungsten electrode tip. The electrode core diameter is 127 μm with a 3 μm insulation layer. The tungsten microelectrode was used to compare artifacts in MR imaging against the CNT electrode.

Figure 4.

(A) Three orientation MR images of electrode embedded in agar phantom, arranged as projections, with arrows indicating the projection slice locations. (B) The optical image of same electrode, to scale. Only the lower tip of the electrode (cross-bar in side profile) is inserted into the brain. Notice the clean edges of the electrode tip. The black dipole voids are from air bubbles that attached to the insulation during phantom preparation.

Figure 5.

Simultaneous bilateral comparison of local field potential signals and neuronal bursts from a rat *in vivo* using (A) a commercial linear array probe and (B) a CNT electrode under 1.6% isoflurane in time, as well as an ex vivo noise floor. (C) Comparison of the frequency profiles of the electrodes.

Figure 6.

Example of multiple-slice anatomical (left column), matched mean EPI images (center column), and seed-based resting-state connectivity maps generated under 1.7% isoflurane in a rat *in vivo* (right column). For the resting-state maps, the seed location is indicated by the white cross in the right hemisphere, and the color map indicates the cross-correlation strength ($|cc| > 0.5$, $p < 0.05$) with red indicating $cc = 1$ and yellow indicating $cc = 0.5$. Imaging was performed with a CNT neural probe implanted in the left hemisphere (image right). The electrode location is indicated by the red arrows in the images.

Figure 7.

Apparent width of CNT electrodes determined by *in vivo* MRI at 9.4T and an optical microscope for comparison. Electrode images were each measured in the same location 6 times with ImageJ and reported as mean plus-minus standard deviation. A single pixel in the MR images was 78 μm x 78 μm . Samples were imaged in different animals on different days. T₂-weighted imaging was not collected for electrode 1.

Figure 8. FSEMS and GEMS imaging in three orientations showing the implanted CNT electrode (electrode 3 from Figure 7) in the *in vivo* rat brain. The electrode location is indicated by red arrows to aid in viewing.

Figure 9.

Hollow (air core) coaxial cylinder of water in air with $r_i = 80 \mu\text{m}$ and $r_o = 120 \mu\text{m}$. Left – filtered numerical solution, right – error compared to analytical result. The grid is 512×512 at $1.6 \times 1.6 \mu\text{m}$, and the largest difference between numerical and analytical solutions is slightly over 0.3 ppm and concentrated at interface between the coaxial cylinder and surrounding medium.

Figure 10.

Comparison of RMS distortion of static magnetic field across the field-of-view as a function of susceptibility difference (left) and diamagnetic film thickness (right). The surrounding medium is water with volume susceptibility of -9.05 ppm. For simulations as a function of susceptibility, the rectangular probe is 401.2 μm wide and consists of three layers: 76.8 μm polyimide, 16 μm film of varying susceptibility, and 76.8 μm PDMS. 254 and 127 μm diameter cylinders were also simulated as a function of susceptibility. The object axis is orthogonal to the static magnetic field in all cases. The 401.2 μm edges of the rectangular probe cross section are perpendicular to the field in orientation 1, and parallel to the field in orientation 2. For plotting distortion vs. film thickness, the probe described above was used but the susceptibility difference between the film and medium was set at -70.95 ppm (-80 ppm absolute) and the thickness was varied. The diamagnetic film alone (without polyimide and PDMS) was also simulated as a function of thickness. Probe orientation 2 produces less field distortion than other geometries. Further, the diamagnetic (-80 ppm) film is primarily responsible for the field distortions around the probes, as simulations of the film alone produce nearly identical results to simulations of the film surrounded by polyimide and PDMS.

Figure 11.

Comparison of simulations (A–H) and experimental data (I–L). Simulated magnetic field distortion caused by the presence of (A) rectangular probe of $76.8\ \mu\text{m}$ polyimide, $9.8\ \mu\text{m}$ of $\chi = -20$ ppm diamagnetic film, and $76.8\ \mu\text{m}$ PDMS; (B) same properties as (A) except diamagnetic film of $\chi = -40$ ppm; (C) silver wire of diameter $254\ \mu\text{m}$; (D) tungsten microelectrode of diameter $127\ \mu\text{m}$. Inserts in upper right corner illustrate the simulated geometries to scale. (E–F) Simulated T_2^* signal weighting calculated from voxel inhomogeneity maps generated by (A–D) using $TE = 4.71$ ms; background brightness level and range matched across images. Experimental T_2^* -weighted (GEMS) images of (I–J) adjacent slices of CNT prototype electrode cross section, (K) silver wire of diameter $254\ \mu\text{m}$ and (L) tungsten microelectrode of diameter $127\ \mu\text{m}$ suspended in agar phantoms. Probe axis is perpendicular to the static field in all cases and scale bars are $445\ \mu\text{m}$.