Safety of Human MRI at Static Fields Above the FDA 8T Guideline: Sodium Imaging at 9.4T Does Not Affect Vital Signs or Cognitive Ability

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Abstract

Purpose: To assess whether exposure to a 9.4T static magnetic field during sodium imaging at 105.92 MHz affects human vital signs and cognitive function.

Materials and Methods: Measurements of human vital signs and cognitive ability made before and after exposure to a 9.4T MR scanner and a mock scanner with no magnetic field are compared using a protocol approved by the United States Food and Drug Administration.

Results: Exposure to a 9.4T static magnetic field during sodium imaging did not result in a statistically significant change in the vital signs or cognitive ability of healthy normal volunteers.

Conclusion: Vital sign and cognitive ability measurements made before and after sodium imaging at 9.4T suggest that performing human MRI at 105.92 MHz in a 9.4T static magnetic field does not pose a health risk.

Key words: MRI safety, ultra-high field MRI, static magnetic field, human vital signs, cognitive function, sodium imaging

INTRODUCTION

The United States Food and Drug Administration (FDA) currently classifies magnetic resonance (MR) scanners with a static magnetic field of 8 Tesla (T) or lower as non-significant risk devices (1). MR devices that utilize a static field in excess of 8T cannot be used for human research or applications without FDA and Institutional Review Board (IRB) approval. The improved sensitivity of MR imaging available with an ultra-high static magnetic field has led to the development of human MR scanners with a static field above 8T. However, due to the small number of devices with a static magnetic field stronger than 8T and a bore large enough to accommodate a human volunteer, there are very limited data available on the effect magnetic fields above 8T on human health. This study reports on the safety of human exposure to a 9.4T static magnetic field during sodium imaging at 105.92 MHz. Vital sign and cognitive ability measurements taken before and after exposure to a 9.4T MR scanner and a zero field mock MR scanner are compared using an FDA and IRB approved protocol.

Over the past two decades the largest static field strength of human MR scanners has increased from less than 2T up to the first 8T system in 1998 and the first 9.4T system in 2004. As human safety data from these scanners became available, the FDA guideline for the static magnetic field of a non-significant risk MR device has increased as well, being set at 2T in 1982, revised to 4T in 1997, and revised again in 2003 to the current 8T limit. Multiple human safety studies have been completed at the current 8T guideline (2-6) with no evidence being reported for statistically significant changes in vital signs or cognitive abilities due to magnetic field strength. No experimental study of human safety above 8T has been reported.

Ultra-high field animal systems have been commonplace for many years, with current animal experiments routinely performed at 7T, 9.4T, 11.7T, and higher. Experimental studies have been conducted on samples ranging from cells to whole animals to assess the risks for exposure to a large magnetic field (2, 7-10). To date, there is no conclusive evidence that prolonged or repeated exposure to an ultra-high static magnetic field has a statistically significant adverse effect on animals. Although it would be presumptuous to extrapolate these findings to human subjects, the current belief is that exposure to magnetic fields up to 8T do not pose a risk to human health (3,7,11,12).

MATERIALS AND METHODS

This study utilized a 9.4T MR scanner that was custom built for human imaging. The 9.4T magnet (GE Healthcare, Abingdon, UK) has a clear magnet bore of 80 cm. This is equipped with a head gradient set (GE Healthcare, Abingdon, UK and Florence, SC; amplifiers by Copley Controls Corp., Canton, MA) and high-order shim set (GE Healthcare, Abingdon, UK and Florence, SC; amplifiers by Resonance Research, Inc., Billerica, MA) that result in a bore access of 36 cm at isocenter, widening to 80 cm at 18 cm from isocenter. The operator interface and control electronics (Bruker Biospin, Billerica, MA) provide full proton and non-proton imaging capabilities with real-time specific absorption rate (SAR) monitoring on up to six independent exciter channels. Only the 9.4T static magnetic field is outside of the current FDA guidelines for non-significant risk MR devices. The FDA approved an investigational device exemption (IDE) to perform this study under IRB supervision. In addition to the 9.4T MR scanner,

a mock MR scanner with no magnetic field was used as a control. All participants of the study were exposed to both the 9.4T MR scanner and the mock MR scanner.

Informed consent was obtained from 25 healthy normal volunteers (12 male, 13 female) between the ages of 18 and 63 years (mean 30.8 years). Volunteers having a medical implant (e.g., pacemaker, aneurysm clip, cochlear implant, neurostimulator, etc), known or suspected pregnancy, claustrophobia, or other contraindication to MRI were excluded from the study. Fifteen of the volunteers reported having had at least one MRI prior to this study. Of those fifteen, five volunteers had a high level of familiarity with MR scanners. Volunteers were required to complete a standard MR screening form prior to acceptance into the protocol and were asked to remove all metallic objects and to change into a hospital gown. Before entering the 9.4T MR scanner, volunteers were checked for metallic objects using a metal detecting wand (Garrett Metal Detectors, Garland, TX).

Neuropsychological testing was performed on each volunteer to assess cognitive abilities. Working memory was measured using the Letter Number Sequencing (LNS) subtest from the third edition of the Wechsler Adult Intelligence Scale (13). For this test, a combination of letters and numbers (e.g., “6P2D”) were verbally presented and the volunteer was asked to recite the numbers in ascending order followed by the letters in alphabetical order (e.g., “26DP”). Written and oral forms of the Symbol Digit Modalities Test (SDMT) (14) were used to assess information processing speed. In the written version, the volunteer filled in numbers, 1 through 9, that correspond with symbols according to a key provided at the top of the page. In the oral version, the examiner recorded the numbers spoken by the volunteer. Each participant was asked to decode

as many symbols as possible from a random sequence in 60 seconds. Immediate memory, delayed memory, and learning were assessed with the Revised edition of the Hopkins Verbal Learning Test (HVLT-R) (15). Twelve words were verbally presented three times. Volunteers were asked to recite all the words that they could recall following each presentation and again after a 25-minute delay. Sustained attention was measured on 21 of the 25 volunteers using the Gordon Diagnostic System (GSD) (16). Volunteers were shown a series of digits, one at a time, and were instructed to press a button every time they observed a "1" followed by a "9". The nine-item Brief Fatigue Inventory (BFI) (17) was administered to assess severity of fatigue and fatigue related impairment. Neuropsychological testing was administered in a private, quiet room at three different times. Each testing session required approximately 30 minutes. Baseline testing was performed prior to exposure to the 9.4T and mock scanners. Neuropsychological testing was performed again after exposure to the 9.4T and mock MR scanners, respectively. To minimize learning, each of the three testing sessions utilized a unique or alternate version of each test, except for LNS and GDS. The neuropsychological tests were scored after all tests within a session were complete. Volunteers were not provided any feedback regarding their performance.

Vital sign measurements were taken with the volunteer positioned at various locations relative to the isocenter of 9.4T and mock MR scanners, respectively. These locations correspond to different measured magnetic field strengths. Non-invasive measurements of heart rate, blood pressure, peripheral arterial O_2 saturation, end-tidal CO_2, respiratory rate, and skin temperature (measured on the forehead) were made using an MR compatible patient monitoring system (InVivo Research, Orlando, FL) with

the volunteer in a supine position. A four-lead electrocardiogram (ECG) measurement was made to assess heart function.

Non-invasive baseline measurements of heart rate, blood pressure, peripheral arterial O_2 saturation, and respiratory rate were made using the equipment described above with the volunteer in a sitting position. Core temperature was also measured in the ear (Braun GmbH, Kronberg, Germany). After initial neuropsychological testing at the Earth's magnetic field, the 9.4T and mock scanner procedures summarized in Table 1 were completed. The order of exposure to the 9.4T MR scanner and the mock MR scanner was randomized and counterbalanced. All volunteers wore 30 dB noise-reducing earplugs during both the 9.4T and mock MR scanner procedures. For each "vital sign measurements" step, three consecutive measurements of vital signs were recorded. Volunteers were moved through the magnetic field of the 9.4T scanner at a constant rate of less than 4 cm/s. This speed has been found to minimize the gustatory, visual, and vestibular sensations associated with moving through a large static magnetic field.

Sodium imaging at 9.4T was performed using a custom-built 26 cm modified birdcage RF coil (GE Healthcare, Applied Science Laboratory, Milwaukee, WI) tuned to 105.92 MHz. Linear and high-order shimming was manually performed at the sodium frequency to obtain a global line width on each volunteer of less than 35 Hz. A line width of 20-25 Hz was often achieved. Imaging was performed using a modified twisted projection imaging (TPI) acquisition (18). The acquisition differed from a traditional TPI scheme in that it incorporated calibration trajectories to precisely determine the center of k-space and had gradient waveforms designed to account for scanner slew-rate

limitations with minimal compromise to the theoretical k-space trajectory. Various acquisition parameters were used for sodium imaging: TR=50-200ms, TE=0.260 – 40ms, maximum gradient amplitude of 1.0 mT/m – 4.0 mT/m, maximum gradient slew rate of 1% – 50% of gradient capabilities (3.96 mT/m/ms – 198 mT/m/ms), radial fraction of 0.12 – 0.47, critically sampled FOV=16 cm – 20 cm, isotropic resolution of 2.25 mm – 5.00 mm. SAR was monitored in real-time during all acquisitions. Image reconstruction was performed with a conventional gridding algorithm using a Kaiser-Bessel interpolation function (19). An audio recording of TPI acquisitions was played through headphones for the volunteer during the simulated imaging portion of the mock MR scanner procedure. The volume of the audio was set to be comparable to that experienced during imaging.

All vital sign sensors other than the ECG pad were removed before each neuropsychological testing session.

After the 9.4T and mock scanner procedures were completed, the volunteer was asked whether they experienced any unusual sensations or discomforts including: temperature change, visual disturbances, metallic taste, nausea, vertigo, muscle twitching or tingling, anxiety, sleepiness, unusual smells, or discomfort due to acoustic noise. Volunteers reporting any unusual sensations or discomforts were encouraged to give a detailed account of the experience.

The vital sign data were tested for statistically significant changes using multivariate analysis of variance (ANOVA). Due to the amount of time required for neuropsychological testing, the 9.4T scanner vital sign data were analyzed separately from the mock scanner vital sign data. A two-way ANOVA with repeated measurements

was used to test the significance of measurement time (before imaging, after imaging), and position (outside of magnet room (9.4T procedure only), 2.6 m from isocenter, at isocenter) on heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, peripheral arterial O_2 saturation, end-tidal CO_2, and skin temperature. Each vital sign type was tested at a 95% confidence level. For the 9.4T scanner, the significance of position (<0.5 mT, 0.3 T, 9.4 T) captures the effect of field strength.

The ECGs from each volunteer were reviewed for consistency throughout the experiment.

A two-way ANOVA with repeated measurements was used to test the significance of the order of scanner exposure (9.4T then mock, mock then 9.4T) and testing session (before exposure, following exposure to 9.4T/mock scanner, following exposure to mock/9.4T scanner) on the cognitive performance of the volunteers. The written and oral versions of the SDMT and the immediate and delayed versions of the HVLT-R test were analyzed separately. Each neuropsychological test was tested at a 95% confidence level.

RESULTS

All 25 volunteers completed the experiment protocol without incident. During exposure to the 9.4T scanner volunteers reported that they experienced: a temperature change (4 volunteers), a metallic taste (6 volunteers), vertigo or lightheadedness (18 volunteers), muscle twitching or tingling (2 volunteers), nausea (2 volunteers), visual disturbances (1 volunteer), unusual smells (1 volunteer), anxiety (1 volunteer), and sleepiness (8 volunteers). The experienced discomforts were not of sufficient intensity to cause any volunteer to ask to be removed from the 9.4T MR scanner, withdraw from the study, or

comment on a sensation prior to the exit interview. No volunteers reported any experienced discomforts persisting outside of the magnet room. Two of the four volunteers reporting a temperature change indicated a temperature decrease, one indicated a temperature increase, and one reported, “feeling a draft” when the door to the magnet room was closed. The temperature of the 9.4T magnet room is 18°C, compared to 21°C outside the magnet room. All volunteers that reported experiencing vertigo, lightheadedness, or a metallic taste indicated that the sensation occurred when being moved through the 9.4T static field and that it did not persist once they were stationary inside or outside the magnet bore for several minutes. One volunteer reporting the muscle twitching or tingling stated that several isolated, non-painful muscle twitches were experienced during imaging, but not on every scan and not for any significant duration. The imaging performed on this volunteer had a maximum gradient slew rate of 37.5 mT/m/ms. Higher gradient slew rates were used on other volunteers without any reports of muscle twitching or tingling. The other volunteer reporting muscle twitching or tingling stated that a single non-painful twitch of a leg muscle was experienced near the end of the 9.4T procedure and not during imaging. The volunteer reporting a visual disturbance described seeing “flashes of light” when being moved through the field. There were no reports of discomfort due to acoustic noise during exposure to the 9.4T MR scanner. The peak sound pressure level during imaging, measured 2.6 m from isocenter, was 86 dBA. For comparison, the SPL measured on a 3.0T clinical MR scanner during comparable sodium imaging was 84 dBA and during clinical echo-planar imaging was 99 dBA.

Volunteers reported that during exposure to the mock MR scanner they experienced: a temperature change (4 volunteers), anxiety (3 volunteers), lightheadedness (1 volunteer), sleepiness (12 volunteers), and discomfort due to acoustic noise (1 volunteer). Three of the four volunteers reporting a temperature change in the mock scanner indicated that they felt warmer when positioned at the mock isocenter.

The SAR did not closely approach the current FDA limit of 3.0 W/kg during any of the acquisitions for any of the volunteers. Typical SAR values were less than 1.5 W/kg during imaging.

The results of the multi-variant analysis of the 9.4T scanner and mock scanner vital sign data are shown in Table 2. In eight volunteers technical complications prevented accurate vital sign measurements of skin temperature, end tidal CO_2, and respiration. These data were not included in the analysis. Data were censored only when there was a clear inaccuracy in the measurement (e.g., a skin temperature of 45°C while the corresponding core temperature measured in the ear was 36°C).

As reflected by the position factor of the 9.4T ANOVA, no statistically significant difference in any measured vital sign was observed due to exposure to the 9.4T magnetic field. Likewise, the position of the volunteer in the mock scanner did not cause a systematic change in any vital sign. No statistically significant change in any of the 9.4T vital sign data was found with respect to measurement time. Similarly, no change with respect to measurement time was observed in the heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, or end-tidal CO_2 mock scanner vital sign data. Significant changes in skin temperature ($p < 0.01$) and peripheral arterial O_2

saturation (p=0.011) with respect to measurement time were observed during exposure to the mock scanner. The bore of the mock scanner is open only at one end, which limits airflow and potentially allows for heating over time. An increase from 21.6°C to 27.3°C was measured in the air temperature of the mock scanner bore during one mock scanner procedure while the volunteer was positioned at the mock isocenter.

All ECGs recorded during the mock scanner procedure and those recorded during the 9.4T scanner procedure with the subject outside the magnet room and positioned 2.6 m from isocenter were unremarkable and consistent. Significant distortions were observed in the ECG waveforms recorded while the volunteer was positioned at the isocenter of the 9.4T scanner. Representative ECG waveforms collected during the 9.4T scanner procedure that illustrate these distortions are shown in Figure 1.

Table 3 shows the results of the ANOVA performed on the neuropsychological data. No statistically significant changes in any of the cognitive abilities tested were observed with respect to the order of exposure to the 9.4T and mock scanners. A significant effect was observed with respect to the testing session for the LNS, written SDMT, and delayed memory scale of the HVLT-R. The mean performance on the LNS (scaled average score in each testing session for 9.4T then mock: 10.36, 10.92, 11.17; mock then 9.4T: 10.84, 12.23, 12.69) and written SDMT (average number correct in each testing session for 9.4T then mock: 57.67, 60.50, 65.60; mock then 9.4T: 63.38 64.15 64.08) improved or remained constant with testing session for both exposure order groups, indicating a practice effect for these tests. The opposite was true for the delayed memory scale of the HVLT-R (z-score in each testing session for 9.4T the

mock: -0.53, -2.07 -1.04; mock then 9.4T: -0.67, -1.05, -2.07) where the best average performance was in testing session 1. No change in performance attributable to testing session was present for the GDS, oral SDMT, immediate memory scale of HVLT-R, or BFI.

Figure 2 shows a representative human sodium image collected at 9.4T. The imaging parameters (TR/TE=105/0.26 ms, 4 mT/m maximum gradient amplitude, 0.2 radial fraction, maximum gradient slew rate of 19.6 mT/m/ms) were selected to give a 3 mm isotropic resolution and a total acquisition time of 5 minutes and 56 seconds.

DISCUSSION

No statistically significant changes in heart rate, systolic blood pressure, diastolic blood pressure, end-tidal CO_2, respiratory rate, peripheral arterial O_2 saturation, or skin temperature were observed in human volunteers exposed to a 9.4T static magnetic field and imaged at 105.92 MHz. During exposure to a mock MR scanner with no magnetic field or imaging capabilities, no measured change in heart rate, systolic blood pressure, diastolic blood pressure, end-tidal CO_2, or respiratory rate was detected. A statistically significant change in skin temperature and peripheral arterial O_2 saturation was observed over time during exposure to the mock scanner. Since the mock scanner has no magnetic field or RF capabilities, the change in skin temperature can be attributed to the limited airflow allowed within the mock scanner bore. During one mock scanner procedure, the temperature inside the mock scanner bore increased by 5.7°C while the volunteer was positioned at the mock isocenter. Since this temperature change occurs slowly over the duration of the simulated imaging, it manifests itself as a temporal temperature change rather than positional temperature change. Though statistically

significant, the mean changes in skin temperature (<1.2 °C) and peripheral arterial O_2 saturation (<0.6 %) were small.

Significant ECG waveform distortions were observed during exposure to the 9.4T static magnetic field. The measured ECG waveforms returned to baseline after the volunteer was removed from the 9.4T static magnet field. Such degradations are well known and are consistent with results reported at 1.5T, 4T, and 8T (2, 3, 5, 6).

The order of exposure to the 9.4T and mock scanners did not have a measurable effect on working memory, immediate memory, delayed memory, information processing speed, learning, sustained attention, or fatigue of the human volunteers. Regardless of the exposure order, an improvement in working memory and information processing speed was observed with repeated testing. This indicates that the volunteers improved their performance due to task familiarity. Volunteers demonstrated the best delayed memory at the beginning of the protocol, before exposure to either the 9.4T or mock scanners. A possible explanation for this finding is that repeated contact with a lengthy word list (12 words) created an interference effect that led to a decrease in performance over time. This is consistent with the proactive interference phenomenon, a well-known source of memory inefficiency (20). The absence of a corresponding performance difference with respect to exposure order implies that exposure to the 9.4T static magnetic field had no deleterious effects on memory. Overall, these data indicate that sodium imaging in a 9.4T static magnetic field does not impact cognitive function in a statistically meaningful manner. No cognitive testing was performed during exposure to the 9.4T static magnetic field, limiting the ability of the data to reflect short-term cognitive effects of the 9.4T static magnetic field. Previous

studies completed at 1.5T and 8T have included cognitive testing during magnetic field exposure and found no suggestion of permanent adverse effects (4-6).

Sodium imaging at 9.4T calls for an excitation frequency of 105.92 MHz, at which the power distribution uniformity and dielectric resonance will be similar to clinically approved 3T proton imaging performed at 128MHz. Real-time SAR monitoring indicated that the FDA limit of 3.0 W/kg was not closely approached during sodium imaging at 9.4T. The SAR was less than 50% of this guideline during most acquisitions. The short transverse relaxation of sodium requires a non-Cartesian acquisition that samples k-space starting at the origin. As a result, very low gradient switching rates can be used to minimize the likelihood of peripheral nerve stimulation. Only one volunteer reported any muscle twitching that was potentially due to gradient switching. However, the volunteer indicated that twitching experienced was non-painful and occurred as short, isolated incidents rather than continuously during imaging.

A high quality, 3 x 3 x 3 mm^3 resolution human sodium image can be acquired at 9.4T in less than 6 minutes. This potentially enables applications such as quantitative MR imaging of non-proton species to be completed using protocols acceptable for human subjects.

The most frequently reported discomfort was lightheadedness or vertigo when being moved through the magnetic field (18 of 25 volunteers). Lesser-reported discomforts included a metallic taste (6 of 25 volunteers), nausea (2 of 25 volunteers), and visual stimulation (1 of 25 volunteers). Volunteers indicated that these sensations were primarily experienced when being moved through the static magnetic field of the 9.4T scanner and that the sensations did not persist once they were stationary for

several minutes. To limit these sensations, subjects were moved through that static field at a slow, constant rate and instructed to minimize head movement. The occurrence of these sensations and the accounts of them provided by the volunteers are consistent with those previously reported (2-6, 12).

In conclusion, the combination of the neuropsychological testing results and the absence of any vital sign changes during exposure to the 9.4T scanner suggests that human exposure to a 9.4T static magnetic field does not represent a safety concern. This is in agreement with the numerous human safety studies completed at 8T (2-6) and is consistent with the expectation from an animal study completed at 9.4T (8).

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Table 1: 9.4T MR scanner and mock MR scanner procedures

	Procedure	Location	Field Strength
9.4 T MR Scanner Procedure	1. Vital sign measurements	Outside the magnet room	< 0.5 mT
	2. Vital sign measurements	Outside bore, head 2.6 m from isocenter	0.3 T
	3. Vital sign measurements	Inside bore, head at isocenter	9.4 T
	4. Up to 60 min. of sodium imaging	Inside bore, head at isocenter	9.4 T
	5. Vital sign measurements	Inside bore, head at isocenter	9.4 T
	6. Vital sign measurements	Outside bore, head 2.6 m from isocenter	0.3 T
	7. Vital sign measurements	Outside the magnet room	< 0.5 mT
	8. Neuropsychological testing	Private testing room	0 T
Mock MR Scanner Procedure	1. Vital sign measurements	Outside bore, head 2.6 m from isocenter	0 T
	2. Vital sign measurements	Inside bore, head at isocenter	0 T
	3. Up to 60 min. of simulated imaging	Inside bore, head at isocenter	0 T
	4. Vital sign measurements	Inside bore, head at isocenter	0 T
	5. Vital sign measurements	Outside bore, head 2.6 m from isocenter	0 T
	6. Neuropsychological testing	Private testing room	0 T

The order of scanner exposure was counterbalanced across volunteers.

Table 2: ANOVA p-values for vital sign data

	Mock Scanner		9.4T Scanner	
	Measurement Time	Position	Measurement Time	Position (Field Strength)
Heart Rate (25)	0.342	0.833	0.112	0.866
Systolic Blood Pressure (25)	0.115	0.913	0.492	0.943
Diastolic Blood Pressure (25)	0.934	0.463	0.082	0.607
Respiratory Rate (17)	0.192	0.193	0.139	0.286
Peripheral Arterial O_2 Saturation (25)	**0.011**	0.500	0.831	0.723
End-Tidal CO_2 (17)	0.060	0.439	0.565	0.705
Skin Temperature (17)	**<0.001**	0.259	0.677	0.838

The number of volunteers for each vital sign type is indicated in parentheses. Numbers differ across vital sign types due to some technical difficulties.

Table 3: ANOVA p-values for neuropsychological testing data

	Exposure Order[a]	Testing Session[b]
Letter Number Sequencing (25)	0.235	**0.016**
Symbol Digit Modalities – Written (25)	0.448	**0.001**
Symbol Digit Modalities – Oral (25)	0.263	0.288
Hopkins Verbal Learning - Immediate Memory (25)	0.610	0.053
Hopkins Verbal Learning - Delayed Memory (25)	0.924	**0.022**
Sustained Attention (GDS) (21)	0.611	0.599
Brief Fatigue Inventory (25)	0.124	0.724

The number of volunteers for each neuropsychological test is indicated in parentheses. Sustained attention data were not available from the first 4 volunteers.
[a]Exposure orders: 9.4T scanner then mock scanner, mock scanner than 9.4T scanner.
[b]Testing sessions: before exposure, following exposure to 9.4T/mock scanner, following exposure to mock/9.4T scanner.

Figures

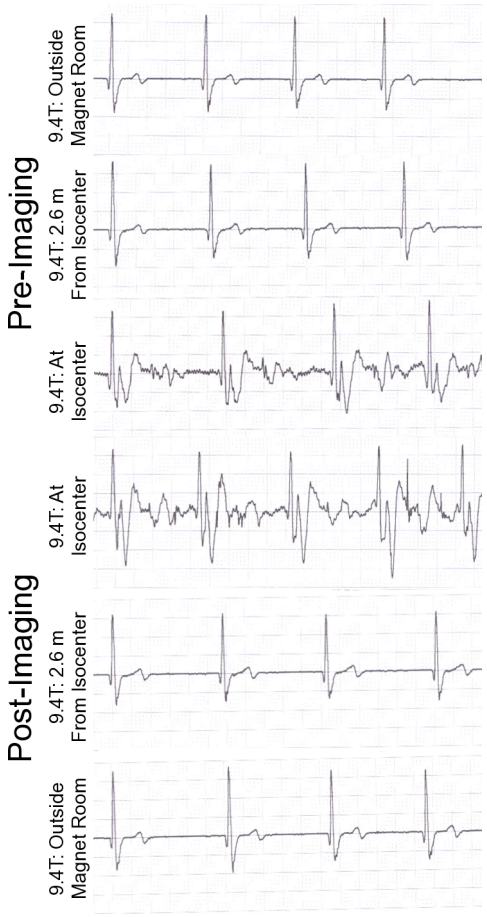

Figure 1: Representative ECG waveforms collected during the 9.4T scanner procedure. Note the significant distortions present with the volunteer positioned at the isocenter of the 9.4T scanner. The occurrence of these distortions is consistent with those reported at much lower magnetic fields.

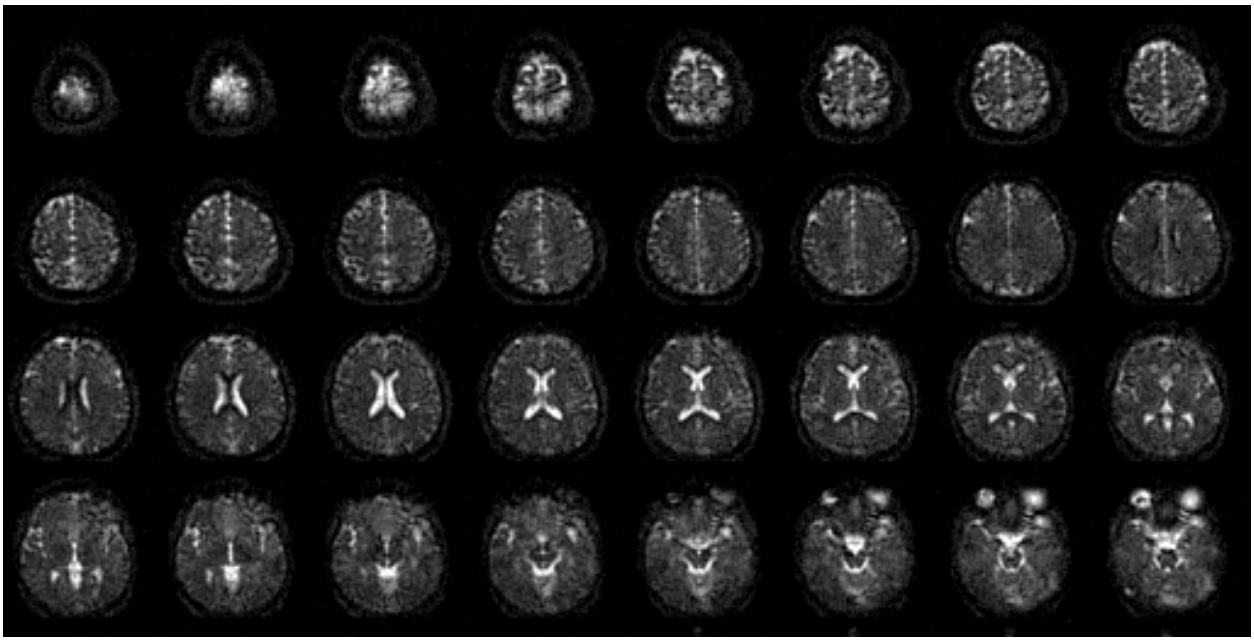

Figure 2: Representative human sodium images collected at 9.4T. The imaging parameters (TR/TE=150/0.26 ms, 4 mT/m maximum gradient amplitude, 0.2 radial fraction, 19.6 mT/m/ms maximum gradient slew rate) were selected to give 3 mm isotropic resolution and an acquisition time of less than 6 minutes.