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HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
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HST-583

Human Subjects in fMRI Research

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1. Human Subjects Issues Specific to Functional MRI

Functional neuroimaging poses some significant risks. Entry into the magnet environment alone is one of those risks. Experiments involving injection of drugs or contrast agents, invasive physiological monitoring, emotionally stressful experimental paradigms, and or use of clinical populations each add additional risks. All aspects of a research career in functional neuroimaging require competence in the area of human subjects protections including clear knowledge of the foreseeable risks, obtaining IRB approval to conduct a study, and informed consent from subjects.

A. Health Effects of MRI Studies

Magnetic Resonance Imaging (including spectroscopy, conventional, and fast imaging techniques) for medical procedures is associated with acceptable and well-controlled risks. However, technological advances in MRI (higher static fields, faster gradients, stronger RF transmitters) have occurred rapidly and many questions regarding the safety of these developments remain unanswered. The standard reference on MR safety is the book by Shellock cited in the references.

Informal market research studies indicate that more than 150 million diagnostic MRI examinations were performed worldwide between the onset of clinical MRI in the early 1980s and the end of 1999; the vast majority of these were conducted without any sign of patient injury. MRI related deaths and injuries are attributable to the high field environment required for scanning, which can result in projectile accidents (AKA “missile effect”). Inadequate screening procedures for metallic objects are the other major factor responsible for subject morbidity and mortality. Examples include the death of a 6 year old boy in 2003 by the projectile path of a metal oxygen tank, and the deaths of patients with cardiac pacemakers who were inadvertently scanned.

Concerns for patient safety have been raised in regard to each of the three distinct fields used in MRI; the static B_0 fields; the radiofrequency (RF) transmission field, B_1 and the time dependent magnetic field gradients.

- **Static B_0 fields- no established adverse health effects.**

Static magnetic fields are measured in Gauss (G) or Tesla (T), with 10,000 G being equal to 1 T. To put things in perspective, the earth's magnetic field varies from approximately 0.3 to 0.7 G between the equator and the poles, respectively. A small refrigerator door magnet may be as strong as 150 G to 250 G. The strengths of the static magnetic fields used in research MR systems for imaging and/or spectroscopy range 0.012 T to over 10 T (100,000 G). According to the most recent recommendations and guidelines provided by the United States Food and Drug Administration (FDA), clinical MR systems in the US are permitted to function on a routine clinical basis at static magnetic field strengths of up to 4.0 T.

Extensive research studies have been conducted in isolated tissues, animals and humans to identify ill effects of exposure to high magnetic fields. While there have been some positive findings, none of these has been replicated. The work performed to date has yet to prove a single example of a scientifically sound and rigorously verified pathological effect of high magnetic fields². The absence of ferromagnetic components in human tissues and the extremely small value of the magnetic susceptibility of these tissues are believed to be responsible for the absence of harmful effects of the high magnetic fields.

Magnetohydrodynamic effects on most body tissues are sufficiently small as to be physiologically insignificant. One hypothesized exception is the endolymphatic tissues of the inner ear that may be the source of sensations of nausea and vertigo reported by some human subjects in the presence of higher

(e.g. 4 to 7T) static magnetic fields. The comfort of subjects will be enhanced by moving them SLOWLY in and out of the magnet and by minimizing their motion while in the magnet.

Note: magnetohydrodynamic forces can induce distortion in recorded ECG signals. It is important to recognize that these distortions do not reflect any change in cardiac conduction; rather they are artifacts in the recording.

The safety aspect of the static field is hard to quantify because there is no clear physical phenomena associated with exposure that can be used to establish upper limits for safe subject exposure. The upper limit on the strength of the static magnetic field that can be used for human imaging studies is set by technical, regulatory and cost factors. Current research efforts to develop ultra high field imaging systems are of high priority. Future work at these higher fields may establish health effects that have not yet been detected.

- **RF B₁ fields- Limiting physiological effect is tissue heating**

A RF pulse (a short burst of an electromagnetic radiation) is used in MRI to "excite" tissue protons by an exchange of energy. The RF spectrum typically used in MRI covers the same frequencies that are used by radio stations (around 100 MHz). Such high frequency oscillations do not elicit peripheral nerve stimulation (see next section).

During MR procedures, the majority of the RF power transmitted for imaging is transformed into heat within the patient's tissue as a result of resistive losses from the induced electric field. This ohmic heating of tissue during MR procedures is greatest at the surface or periphery and minimal at the center of the body of human subjects.

Absorption of RF power by the tissue is described in terms of Specific Absorption Rate (SAR), which is expressed in Watts/kg. In the US, the recommended SAR level for head imaging is 3.2 Watts/kg. The relative amount of RF radiation that an individual encounters during a MR procedure is usually characterized with respect to the whole-body averaged and peak SAR levels (i.e., the SAR averaged in one gram of tissue).

The SAR produced during a MR procedure is a complex function of scanner and body factors. Scanner factors include the frequency (i.e., determined by the strength of the static magnetic field of the MR system, with resonant frequencies producing the greatest effect), the type of RF pulse used (e.g., 90° vs. 180° pulse), the repetition time and the type of RF coil used. Body factors include the volume of tissue contained within the coil, the configuration of the anatomical region exposed, the orientation of the body to the field vectors, as well as other factors. However, the actual increase in tissue temperature caused by exposure to RF radiation is dependent on the subjects thermoregulatory system (e.g. tissue perfusion, etc.). The risk of exposing subjects with compromised thermoregulatory function (e.g. elderly patients and patients taking medications that affect thermoregulation, such as calcium-blockers, beta-blockers, diuretics, or vasodilators) to MR procedures that require high SARs has not been assessed.

When operating a commercially built scanner with coils and pulse sequences provided by the manufacturer, all scanning will be done within safe limits. When developing new coils, pulse sequences or in other ways adapting the scanning environment, it is the obligation of the investigator to ensure that the scans will be safe for human subjects. Several of the newer pulse sequences and imaging techniques that have been developed use relatively high levels of RF energy. For example, using fast spin echo (FSE) and magnetization transfer contrast (MTC) pulse sequences on high-field-strength MR systems may require levels of RF energy that easily exceed whole body averaged SARs ranging between 4.0 to 8.0 W/kg (i.e., higher than the level currently recommended by the FDA). The thermogenic effects of RF energy deposited by the newest ultra high field imaging systems have yet to be characterized.

In order to minimize any excessive tissue heating that may occur during exposure to high levels of RF energy, use the fan in the scanner during imaging procedures whenever tolerated by the subject.

Electrical Burns

RF fields can cause burns by producing electrical currents in conductive loops. When using equipment such as surface coils, ECG or EEG leads, the investigator must be extremely careful not to allow the wire or cable to form a conductive loop with itself or with the subject. Coupling of a transmitting coil to a receive coil may also cause severe burns.

Switched gradient fields- Limiting physiological effect is peripheral nerve stimulation

The thermal effects that result from gradient switching during MRI have been found to be essentially negligible and are not considered clinically significant. Similarly, the stimulation effects on cardiac tissue are considered negligible. However, both theory and practice have demonstrated that gradient magnetic field switching can induce metallic taste, magnetophosphenes (electromagnetically-induced visual flashes of light), peripheral nerve stimulation, and skeletal muscular contractions.

To minimize these electrical effects, subjects should be instructed not to clasp their hands (to avoid creating a conductive loop, thus increasing the likelihood of neural stimulation) and to inform the operator if they experience any discomfort or pain so that they can be re-positioned in the magnet.

The pulsed gradient fields that occur during MRI expose the subject to a time varying magnetic field. According to Faraday's Law of Induction, exposure of any conductive tissue to time-varying magnetic fields will induce an electric field (measured in V/m) in the conductive tissue that is oriented perpendicular to the time rate of change of the magnetic field. These effects are markedly greater using echo planar imaging technology and hardware that requires up to 2.5 gauss/cm maximum amplitudes and <300 microsecond rise times.

The magnitude of the electric field will be determined by several factors including the electrical resistance in the induced circuit in the tissue(s), the cross sectional area of the tissue, and the rate of change (i.e., changing magnitude versus time) of the gradient magnetic field, itself³. All induced electric fields will occur during the times that the gradient magnetic field strengths are changing; the greater the magnitude of the rise and fall times, the greater the induced electric field. And, the steeper the rate of rise of the gradient magnetic field strength, the lower the threshold for peripheral nerve stimulation. The relations between these factors are linear, with a slope unique to each waveform (e.g. sine wave or trapezoid).

Note that there is a greater changing magnetic field over time as one proceeds further away from the center and towards the ends of the gradient coils, where the time rate of change of the gradient magnetic fields is the greatest (AKA maximum magnetic flux). The length of the gradient coils thus determines the site of peripheral nerve stimulation.

Acoustic Noise

Another potentially hazardous effect related to gradient magnetic fields is the acoustic noise produced as current is passed through the gradient coils during image acquisition. For anatomical imaging, the noise is mostly of low frequency and has a "clunking" sound; for EPI, the noise can be of very high frequency (600-1400 Hz) and sounds like a loud "beep". Generally, the stronger gradients

used with higher magnetic fields and with EPI produce more intense noise. Prolonged exposure to this noise will damage the unprotected ear. Even conventional scanning procedures, which are considered to produce noise within the recommended FDA safety guidelines, have been documented to cause reversible hearing loss when patients did not wear ear protection.

All research subjects should wear hearing protection in the form of earplugs or headphones during scanning (both are recommended on the 3T). Earplugs must be the right size and properly inserted into the ear canal to obtain their full effect. This requires instruction and practice. It is the responsibility of the researcher to see that the subject is properly fitted with hearing protection. Packing the subject's head with foam cushions further dampens the noise and is recommended in the 3T environment.

Additional noise in the magnet environment comes from the magnet coolant pump, air handling system and patient fan. While not dangerous, these other sources of noise can be annoying to subjects and can interfere with communication.

B. Safety in the High Field Environment

1. Screening

This is the single most important safety step. No subject with any contraindication to scanning should ever be scanned. All subjects should be thoroughly screened by a trained staff member before recruitment into any imaging study. Preferably before they come to the scanner to avoid wasting precious scan time. Absolute contraindications to scanning include: indwelling ferromagnetic material (e.g. foreign object in eye, some surgical implants), pregnancy, seizure disorder, implanted bioengineering device (e.g. pacemaker, infusion pump), anxiety disorder, weight over 300 lbs.

2. Pre-imaging preparation

When subjects arrive at the scanner they must complete the screening form to verify that they have no contraindications for scanning (see sample form at end of handout). All investigators entering the scanning environment must be similarly screened. Subjects must provide informed consent to participate in the study. Subjects and investigators must remove all metallic objects before entering the scan room, including coins in pockets, watches, wallets, hair pins, safety pins, and make-up.

C. Distress in the MR environment

- Incidence of distress

Distress in the MR environment includes all subjectively unpleasant experiences that are directly attributable to the MR study. The distress of subjects undergoing MR studies can range from mild anxiety that can be managed simply with minimal reassurance, to a full-blown panic attack that may require psychiatric intervention. Severe psychological distress reactions to MR imaging, namely anxiety and panic attacks, are typically characterized by the rapid onset of at least four of the following clinical signs: fear of losing control or dying, nausea, paresthesias, palpitations, chest pain, faintness, shortness of breath, feeling of choking, sweating, trembling, vertigo, or depersonalization. Appropriate screening procedures to exclude susceptible subjects from studies are required. For clinical research studies in which the subject population of interest has an anxiety disorder e.g. claustrophobia, generalized anxiety disorder, post-traumatic stress disorder, or obsessive-compulsive disorder or a cognitive deficit, it is always necessary to use measures to minimize distress.

Research studies on the incidence of anxiety responses to MR imaging have only been conducted on patients undergoing diagnostic procedures. Note that clinical imaging to diagnose or stage disease is inherently distressing. In that population, moderate distress severe enough to be described as a dysphoric psychological reaction has been reported by as many as 65% of the patients examined by MR imaging. The most severe forms of psychological distress described by patients are claustrophobia, and anxiety or

panic attacks. Claustrophobia is a disorder characterized by the marked, persistent and excessive fear of enclosed spaces. In such affected individuals exposure to enclosed spaces such as the MR environment almost invariably provokes an immediate anxiety response that can be indistinguishable from a panic attack as described above.

There are no good predictors of who will experience distress in the MR environment. In fact, different studies cite opposing results such as which gender has greater difficulty tolerating the MR studies. These differences may reflect cultural, socioeconomic or other influences such as the behavior of the research scientist.

Motion artifact disrupting the MR image quality is frequently the result of subject distress. Motion artifacts can compromise the quality of MR image data. A recent clinical study of 297 first-time MR outpatients demonstrated that approximately 13% of all MR studies showed motion artifacts unrelated to normal physiological variables and about half of these impaired the diagnostic quality of the examination. Excessive anxiety with accompanying tremors, trembling, and jaw clenching has been presumed to contribute to motion artifacts in MR images and has even erroneously been reported as functional activation in bilateral temporal lobes in an early PET study.

- Factors that contribute to distress

The physical environment of the MR system can be a source of distress to subjects. Sensations of apprehension, tension, worry, claustrophobia, anxiety, fear, and even panic attacks have been directly attributed to the confining dimensions of the interior of the MR system in the clinical studies (e.g., the patient's face may be three to ten inches from the inner portion of the MR system).

Similar distressing sensations have been attributed to the prolonged duration of the MR examination, the gradient magnetic field-induced acoustic noise, the temperature and humidity within the MR system, and the distress related to the restriction of movement. For example, gradient field induced noise is sufficiently intense to cause transient hearing threshold shifts in as many as 43% of patients undergoing MR procedures. Other studies have reported stress related to the administration of a MRI contrast agent. Additionally, the MR system may produce a feeling of sensory deprivation, which is also known to be a precursor of severe anxiety states.

Adverse psychological reactions are sometimes associated with the MR procedures because the study may be perceived by the patient as a "dramatic" medical test that has an associated uncertainty of outcome (i.e., there is a fear of the presence of disease or other abnormality). For those fMRI studies conducted in clinical research populations, even when subjects are informed that the study is only for research purposes and is not going to affect their treatment or prognosis, they may still have expectations or concerns.

- Techniques to minimize subjective distress

Certain measures to alleviate subject distress should be employed for all studies. A number of other measures will be required if the subject is experiencing significant distress due to factors as described above. Finally, other distress-alleviation techniques will only be necessary for subjects with co-existing psychiatric illness or other special problems.

The single most important step is to educate the subject about the specific aspects of the MR examination that are known to be particularly difficult to tolerate. This includes conveying, in terms that are understandable, the internal dimensions of the MR system, the level of gradient magnetic field-induced acoustic noise to expect, the estimated time duration of the study, and the need to remain still during imaging.

Upon entering MR facility, subjects who are treated with respect and are welcomed into a calm environment will experience less distress. Many details of subject positioning in the MR system can increase comfort and minimize distress. Taking time to ensure comfortable positioning with adequate padding and blankets to ensure no undue pain from positioning is also important. Adequate ear protection should be provided routinely to decrease acoustic noise from the MR system. Demonstrate the two-way intercom system to reassure the subject that the MR staff can hear them when they speak and can speak to them.

Maintain verbal contact via the intercom system or physical contact by having a study staff person remain in the MR system room with the subject during the examination to decrease psychological distress. All subjects should be given a “panic button” that allows them to immediately communicate severe distress. MR system-mounted mirrors or prism glasses can be used to permit the subject to maintain a vertical view of the outside of the MR system in order to minimize phobic responses.

The environment of the MR system may be changed to optimize the management of apprehensive subjects. For example, the presence of higher lighting levels tends to make most individuals feel less anxious. Therefore, the use of bright lights at either end and inside of the MR system can produce a less imposing environment. In addition, using a fan inside of the MR system to provide more air movement will help reduce the sensation of confinement and lessen any tissue heating that may result from RF power deposition during imaging.

Let the Neuroscientist Beware!

The following measures that have been shown to be effective in minimizing subjective distress may not be compatible with your functional imaging studies. The following suggestions should only be employed after careful consideration of the impact they may have on the functional imaging data to be collected. (Consider why)

Some MR staff have reported that placing a cotton pad moistened with a few drops of essential lemon or vanilla oil or other similarly used form of aroma therapy in the MR system close enough so that the subject may receive olfactory stimulation can also reduce distress. Electronic devices that utilize compressed air to transmit music or audio communication through headphones have been developed specifically for use with MR systems. MR-compatible music/audio systems may be acquired from a commercial vendor or can be made by adapting an airplane pneumatic earphone headset. MR-compatible music systems can be used to provide calming music to the subject and, with the proper design, help to minimize exposure to gradient magnetic field-induced acoustic noise. Reports have indicated that the use of these devices has been successful in reducing symptoms of anxiety in subjects during MR procedures. In addition, it is now possible to provide visual stimulation to the patient via a projection television.

Additional measures such as pre-imaging behavioral therapy, hypnosis and sedation have been successfully employed for clinical imaging studies that are essential for diagnostic purposes (see discussion in ¹ for full details).

2. Ethical Conduct of fMRI Research involving Human Subjects

A. Investigator Training

It is the responsibility of every investigator who conducts research with human subjects, healthy or otherwise, to be fully informed about and to practice current standards of good clinical practice. It has

been said, “ignorance is blameworthy”. This information is widely available and each institution has an office to assist you. Harvard, HMS (<http://www.hms.harvard.edu/integrity/>) and MIT all have official policy statements regarding the responsible conduct of research. **Read them. Practice safe research.**

You are responsible for understanding the rights of your human subjects and the requirements for obtaining true informed consent. You can peruse the federal Office for Human Research Protections website. Required reading includes:

1- The Belmont Report: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

2- Title 45 Code of Federal Regulations Part 46 Protection of Human Subject

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

You may choose to complete the Collaborative IRB Training Initiative (CITI) human subjects research educational program. The CITI offers many advantages, primarily the depth and breadth of information pertaining to human-subject research and the case-based application of ethical concepts and regulations in a web-based learning environment. You can register for the CITI program through <https://www.citiprogram.org/default.asp>.

B. Critical Elements to Informed Consent

There can be no element of coercion in the recruitment of research subjects. All subjects have the “right” to say no. For example, in the setting of a lab director asking a trainee to participate in a study, the right to say “no” is violated by the conflict generated by the director’s position of authority over the trainee.

All risks must be clearly specified in the consent. For a typical fMRI study at either 1.5T or 3T, the information that is required includes the following:

“There are no known or foreseeable risks or side effects associated with conventional MRI procedures except to those people who have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers) or to those who have clips on blood vessels in their brain. There are no known additional risks associated with high-speed MRI. Both the conventional and the high speed MRI systems have been approved by the FDA and will be operated within the standards reviewed and accepted by the FDA.

A magnetic resonance scan is not uncomfortable. You will lie on a table that slides into a horizontal cylinder that is only slightly wider than your body. You will be asked to lie still, but you will easily be able to hear and speak to the research staff. The MR scanner makes loud knocking or beeping sounds during imaging; earplugs will be provided to help reduce this noise. There should not be any significant discomfort during this procedure. If you notice any discomfort you should notify the investigators as soon as possible. If the discomfort cannot be reduced to an acceptable level, the scanning session may be stopped. The MRI can be stopped at any time at your request. If you are prone to claustrophobia (fear of enclosed spaces) you should notify the course director in charge of the scan. If you are or might be pregnant, it is recommended that you do not participate in this MRI study.”

C. Risk/Benefit Considerations

Over the past several years the bar has been raised in terms of the allowable risk/benefit ratio for IRB approved studies. For example, it is no longer possible to get federal funding or IRB approval for studies to expose patients to the risks of imaging solely to learn about the underlying scientific basis of the disorder. Instead, the investigator must demonstrate how the outcome of the study will directly impact the clinical care of that study population. This is true not only for clinical trials of potential new treatments, but also for pharmaceutical challenge studies.

It is incumbent upon each investigator to determine all potential risks or adverse outcomes from a proposed study and to establish that the benefit to society will sufficiently outweigh the risk to the participating individuals.

Case Study:

Intraoperative Registration of Medical Images by Temporarily Implanted Fiducial Markers

You have been diagnosed with an operable brain tumor. In order to identify the size, location, and margins of the tumor, a stereotactic frame has been affixed to your skull. You will be having MR and CT imaging studies done with the frame in place and then later will have your surgery. The frames are terribly bulky and uncomfortable, quite invasive, very unsightly, and can interfere with optimal imaging. The neurosurgeon has approached you about participating in a research study in which small fiducial markers will be anchored to your skull and will remain in place for the imaging and surgical portions of your medical care. You are given a consent form that describes the procedure by which the markers will be implanted. The consent includes information that the markers themselves have no known adverse health effects.

1. What questions do you have for your physician?

2. What are your concerns? Do you express them to your physician? If so, what do you say?

3. Would you agree to participate in this study? If so, why? If not, why not? If undecided, what additional information do you need to make a decision one way or the other?

4. If you were an Institutional Review Board (IRB) member, would you have any additional concerns or questions for the investigators in order to determine whether you would approve this research protocol and/or the consent form?

References and Further Information

Websites offering regulatory information, education modules, institutional compliance programs and other educational material and resources.

The FDA's website: <http://www.fda.gov/>

And their links to very useful sites: <http://www.fda.gov/oc/gcp/default.htm>

AAMC Research Integrity website

<http://www.aamc.org/research/clinicaltrialsreporting/start.htm>

NIH (DHHS) Bioethics resources on the web

<http://www.nih.gov/sigs/bioethics>

AHC's with electronic tutorials and other resources

<http://www.research.umn.edu/consent/>

Martinos Center

<http://www.nmr.mgh.harvard.edu/martinos/userInfo/human/index.php>

MRI Specific

<http://www.MRIsafety.com>

http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_38.htm

<http://www.nmr.mgh.harvard.edu/martinos/userInfo/safety/index.php>

A CHECKLIST FOR ETHICAL DECISION-MAKING¹

- STEP 1 Recognize and define the ethical issues (i.e., identify what is (are) the problem(s) and who is involved or affected).
- STEP 2 Identify the key facts of the situation, as well as ambiguities or uncertainties, and what additional information is needed and why.
- STEP 3 Identify the affected parties or "stakeholders" (i.e., individuals or groups who affect, or are affected by, the problem or its resolution). For example, in a case involving intentional deception in reporting research results, those affected include those who perpetrated the deception, other members of the research group, the department and university, the funder, the journal where the results were published, other researchers developing or conducting research on the findings, etc.
- STEP 4 Formulate viable alternative courses of action that could be taken, and continue to check the facts.
- STEP 5 Assess each alternative, (i.e., its implications; whether it is in accord with the ethical standards being used, and if not, whether it can be justified on other grounds; consequences for affected parties; issues that will be left unresolved; whether it can be publicly defended on ethical grounds; the precedent that will be set; practical constraints, e.g., uncertainty regarding consequences, lack of ability, authority or resources, institutional, structural, or procedural barriers).
- STEP 6 Construct desired options and persuade or negotiate with others to implement them.
- STEP 7 Decide what actions should be taken and in so doing, recheck and weigh the reasoning in steps 1-6.

REFERENCES

¹From Swazey, Judith P. and Bird, Stephanie J. (1995) Teaching and Learning Research Ethics. *Professional Ethics* 4: 155-178, Weil, Vivian (1993) Teaching Ethics in Science in *Ethics, Values and the Promise of Science*, Research Triangle, Sigma Xi, 243-248, and Velasquez, M. (1992) *Business Ethics* (3rd ed.) Englewood Cliffs: Prentice Hall.

*** Sherlock, FG ed., Magnetic Resonance Procedures: Health Effects and Safety, CRC Press, Boca Raton, 2001 (and more recent editions)**

*** On Reserve**

*1. Gollub, R. L. and F. G. Sherlock, Claustrophobia, anxiety, and emotional distress in the magnetic resonance environment, in *Magnetic Resonance Procedures: Health Effects and Safety*, F.G. Sherlock, Editor, CRC Press, Boca Raton, 2001, p. 197-216.

2. Schenck, J. F., Safety of strong, static magnetic fields. *Journal of Magnetic Resonance Imaging*, 12: 2-19, 2000.

3. Schmitt, F. Physiological side effects of fast gradient switching, In *Echo-Planar Imaging: Theory, Technique and Application*, F. Schmitt, M.K. Stehling and R. Turner.

I haven't read this but it looks good if you want more information on the interface between MRI technology development and safety/practical considerations:

Hecht EM, Lee RF, Taouli B, Sodickson DK. Perspectives on body MR imaging at ultrahigh field. *Magn Reson Imaging Clin N Am*. 2007 Aug;15(3):449-65, viii.

PMID: 17893062