Symptoms and Cognitive Effects of Exposure to Magnetic Stray Fields of MRI Scanners

Gezondheidsklachten en cognitieve effecten door blootstelling aan magnetische strooivelden van MRI scanners.

(met een samenvatting in het Nederlands)

Proefschrift

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Frank Gérard de Vocht
geboren op 15 januari 1978
te Boxmeer, Nederland

Promotor: Prof. Dr. Ir. D. Heederik

Co-promotoren: Dr. Ir. H. Kromhout
Dr. J.M.L. Engels

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THE PLAN IT WASN'T MUCH OF A PLAN
I JUST STARTED WALKING

From: “Nothing Really Ends” on the album “Pocket Revolution”, dEUS, 2005

de Vocht, F.G., 2006
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Chapter 1

GENERAL INTRODUCTION

BACKGROUND

Humans can be exposed to non-ionizing electromagnetic fields originating from anthropogenic sources superimposed on the Earth's natural magnetic field (varying between 25 and 65 μT)[1-3]. Such exposure can occur in the general environment[4,5] as well as in occupational settings[6].

The discussion whether exposure to magnetic fields has an impact on biological tissue has a long history, and written evidence on its medical applications exist already from the Roman period (Pliny the Younger, 62-114 AD)[7]. The German physician and alchemist Paracelsus (Philippus Theophrastus Aureolus Bombastus von Hohenheim (1492-1541))[8] promoted the therapeutic powers of powdered magnetic iron oxides already in the 16th century. He was however opposed by William Gilbert[9], who argued that using a magnetic lodestone powder would weaken its magnetic influence to the vanishing point[10,11].

Another important historical figure was the Switzerland born physician Franz Anton Mesmer (1734-1815), who became extremely successful through his *animal magnetism* practice in Paris[12]. However, a committee appointed by Louis XIV concluded that the clinical improvement among his patients were the result of his ability to manipulate their imaginations and not the use of magnets.

It was however not until the end of the Nineteenth century that the first effects of electromagnetic radiation on biological organisms (description of phosphenes in man) were observed by Jacques Arsène d'Arsonval (1851-1940) in 1896 and Nikola Tesla (1856-1943) independently[7].

The controversy has continued to exist to the present time[13]. New applications of magnetic fields have been found in the use of magnetic bracelets[14,15] and necklaces, and as a therapy for pain relief[16]. At the same time, evidence based applications like transcranial magnetic stimulation (TMS)[17-19] have emerged as possible treatments for depression and Parkinson's disease, and, to a lesser extent, schizophrenia, obsessive-compulsive disorder among others[20,21].

The discovery of Nuclear Magnetic Resonance (NMR) in 1946[22] led initially to applications to determine chemical compositions of materials. In the 1970s it resulted in the introduction of Magnetic Resonance Imaging[1] (the word nuclear was intentionally dropped to avoid scaring patients) (MRI)[23,24], which has evolved into a major routine medical imaging technique and tool for in vivo biomedical research from the 1980s onwards[25,26].

MAGNETIC RESONANCE IMAGING

MRI is an imaging modality, which makes use of electromagnetic fields and provides detailed images of soft tissue and is therefore very well suited for anatomical imaging. Image contrasts are the result of differences in water binding, concentration of macromolecules in tissue, concentration of iron containing molecules, and others. Furthermore, it can also be used to measure dynamic physiological processes like blood flow, tissue perfusion or changes in blood oxygenation, beating of the heart, digestion of a meal, among others[26].

MRI is based on the concept that due to the magnetic moment of nuclei, when placed in a magnetic field, they have a fixed energy status, which is dependent on the Larmor frequency of the nuclei. This frequency, also referred to as the precession (spinning) frequency, depends on the nucleus itself, but also on local factors such as the applied magnetic field strength and the chemical environment of the nucleus. By applying a short radio frequency (RF) pulse (at the same, and thus resonant, frequency as the nuclei are spinning), the energy status of the nuclei can be raised temporarily (the nuclei are exited). When the pulse is stopped, the nuclei will return (relaxate) to their original energy status (with specific relaxation times T_1 and T_2) which will induce a voltage that can be registered. To code for spatial position of the signal a small spatial gradient magnetic field is applied superposed to the homogeneous static magnetic field.

The magnetic field strength (H) is expressed in Ampère per meter (A/m). The total number of lines of magnetic force in a material is called the magnetic flux, which is expressed in the unit of a Weber (Wb) ($1x10^8$ field lines). The number of magnetic lines of force cutting through a plane of a given area at a right angle is known as the magnetic flux density (B) and is expressed in Tesla (T) (1 Wb/m^2) or in Gauss (G) ($1x10^{-4}$ Tesla).

An MRI system consists of a large superconducting magnet to generate a strong static magnetic field (B_0). For whole-body MRI systems, magnetic flux densities are usually divided into low field (0.2-1.0 Tesla), high field (1.0-3.0 Tesla), very high field (3.0-7.0 Tesla) and ultra

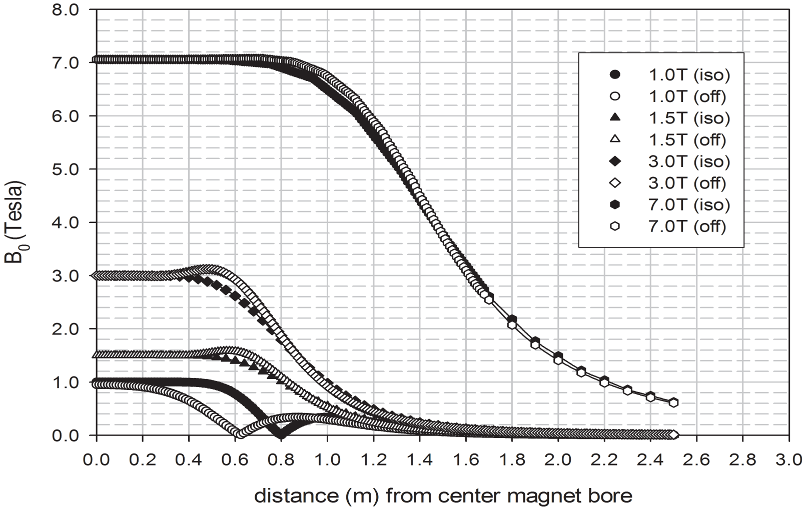

Figure 1.1. Measured static magnetic fields (B_0) for various cylindrical and open (1.0T) magnets along a line through the iso-centre, or 50cm (1.0T) or 25 cm from the magnet centre.

high field (>= 7 Tesla)[27]. In addition to the homogeneous static magnetic field in the magnet borehole, gradient coils generate a small gradient magnetic field (in the order of 20 mT/m switched in 1 millisecond for routine systems, although systems with higher performance have been developed) in all three orthogonal directions and allow for spatial coding of the MR signal. Furthermore, radio frequency (RF) coils generate RF pulses (10-20 μT) and register the MR-signal.

Most MRI systems apply a cylindrical magnet, but modern low field systems also may have a bipolar vertical magnetic field (the so-called open systems)[28]. In the centre of the magnet bore the generated magnetic field is as homogeneous as possible in all three directions ($dB_0/dx_{\text{for } x=x,\ x=y \text{ and } x=z}$), while a spatial gradient is present near the edges of the bore. This magnetic gradient field extends to the area surrounding the magnet (spatial magnetic stray field). The magnetic flux density of this stray field is inhomogeneous, depending on characteristics of the MRI system and is in general characterized by a rapid drop off with distance from the magnet (Figure 1.1). The flux density of the stray field at a specific position can be expressed as a spatial magnetic gradient (dB_0/dx) and the measured gradient fields at different spatial positions along a line through the iso-centre and along a line 25 cm from the

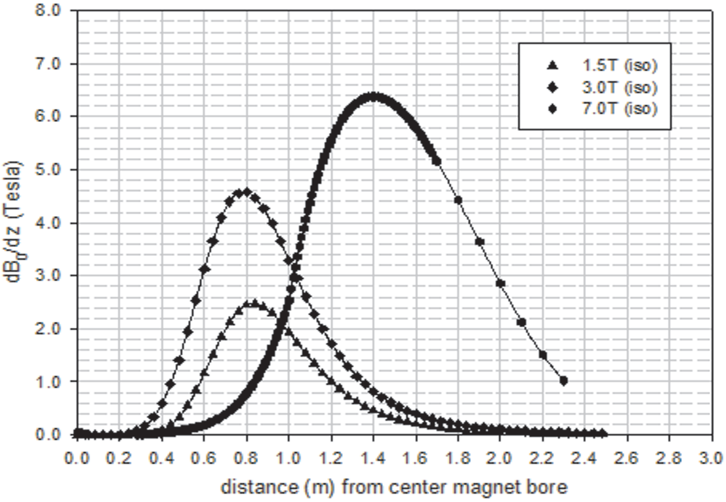

Figure 1.2a. Measured static magnetic gradient fields for various cylindrical and open (1.0T) magnets along a line through the iso-centre.

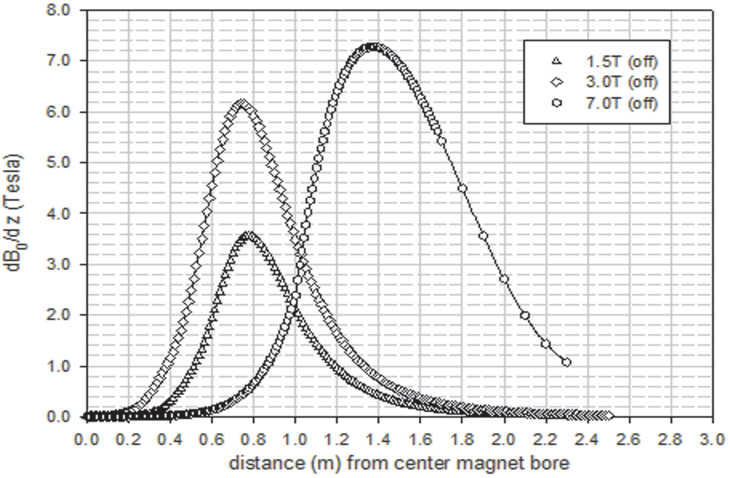

Figure 1.2b. Measured static magnetic gradient fields for various cylindrical and open (1.0T) magnets along a line 25 cm from the magnet.

magnet centre are shown graphically for several cylindrical and open MR-systems in Figures 1.2a and 12.b.

Magnet shielding is used to limit the distance from the magnet where strong magnetic fields are still present by either a metal box around the magnet (i.e. in the walls of the room to avoid strong magnetic fields in adjacent rooms or corridors), or actively, by building a second magnet with opposite field orientation on the outside of the main magnet[27].

In actively self-shielded magnets however, the magnetic field strength at the edges of the bore can be somewhat greater than the field strength at the magnet's isocenter[29] (see Figure 1.1 for the 1.5 T and 3.0 T magnets). Furthermore, at present technical limitations prohibit actively self-shielded magnets at ultra-high field, although it is expected that self-shielded 7 T systems will become available within a few years[25].

EXPOSURE TO ELECTRO-MAGNETIC FIELDS IN MRI

At present approximately 20.000 MRI-systems routinely operate at 0.5 to 3.0 T in the clinical setting world-wide, with most systems operating at 1.5 T (~70%). Presence in, or near, these systems exposes patients as well as engineers and medical staff to both a large static field (B_0), a spatial magnetic gradient outside the magnet (dB_0/dx), and a time-varying field (dB_0/dt) induced by moving through the spatial magnetic stray field. During scanning, patients and sometimes employees are also exposed to time-varying fields in the milliTesla (mT) range from spatial gradient fields that are switched on and off rapidly, as well as an RF field that exposes them to extremely rapidly varying fields in the µT range[26].

The largest group of occupationally exposed workers are radiographers[26], who operate the scanner and look after the patient's comfort and safety. Consequently, they need to lean into the magnet bore and walk in the stray field regularly. Furthermore, radiologists are responsible for the clinical quality of the scanning process, and enter the static field in the same way as radiographers, in particular to administer contrast agent if required. Anaesthesiologists are also sometimes involved in scanning patients and will be in the proximity of patients during scanning.

Studies have shown[30,31] that MRI operators are regularly exposed to fields up to 5 mT, but exposure to 100-150 mT could already easily be achieved while in the vicinity of a 0.02 or 0.5 T clinical MRI system. A trend towards an increase of interventional MRI procedures however, will greatly increase the duration of exposure of radiologists, anaesthesiologists and operating teams to magnetic fields, including the gradient and RF fields in the mT-range from other equipment in the operating room[32], as they will inevitably have to be near the patient during scanning.

Outside the clinical setting, engineers involved in constructing, testing and maintaining the scanners are also exposed to static magnetic fields. Furthermore, physicists, engineers and development staff might potentially also receive considerable exposure since they often use novel systems or use standard scanners in non-standard ways[26]. Finally, to optimize systems or settings it is often necessary to use human volunteers because test phantoms can only adequately mimic a fraction of the human body and are certainly not suitable to mimic human physiology (including respiration, heart beat, blood flow, perfusion and diffusions of body liquids etc.).

Small-bore magnets are used to scan animals and other objects in research institutions, and they are used in the pharmaceutical industry where imaging allows the time course of the effect of the drugs to be studied. Although often of higher static field strength (~7T) than clinical scanners, the smaller bore (~30cm) makes it harder for staff to expose more than a small part of their bodies to high field strength[26].

Exposure to static magnetic fields is also found in other occupational settings, but at lower intensity. Workers in the aluminium production and chloralkali industry are exposed to fields ranging from 4 to 5 mT. Railway workers on train systems operating from DC power supplies are exposed to fields up to 50 mT[31], and some welding processes also produce static magnetic fields in the μT range[6,33,34].

TRENDS

At present two main trends are driving the development of new MRI systems[25,26]. In all applications a drive towards the use of higher magnet fields is present. While imaging of humans was first achieved at 0.04 T[35], the current routine MRI magnetic field strength is 1.5 T[13]. 3 T systems however, are rapidly replacing 1.5 T systems, and even ultra-high field magnets (>7 Tesla) have started to appear[25,26]. For experimental animal research, 9.4 Tesla systems are becoming the standard, but a first 11.7 T system was already operational in 2004[25]. Trends in functional MRI studies and interventional MR are also towards higher field strength[25,36].

Higher field strengths are associated with a better "signal to noise"-ratio in an image, which can be used to increase spatial resolution and reduce imaging time. The shorter imaging time can be used for shorter examination time, but also for dynamic studies of changing systems such as functional MRI studies and in MR angiography. Secondly, higher fields lead to an increased NMR relaxation time, which is an advantage in studies to measure blood flow or tissue perfusion using blood as an intrinsic contrast agent[26].

A second important trend is an increase in the development and use of MRI systems for interventional procedures with both open and closed MRI systems, which allow medical staff to perform therapeutic and diagnostic procedures on a patient[28], while simultaneously being guided by MRI[37-45] (Figure 1.3). At present, MRI systems for interventional procedures do not exceed 0.5 Tesla[37], although combinations of MR suites with operating rooms exist at higher field strengths[46].

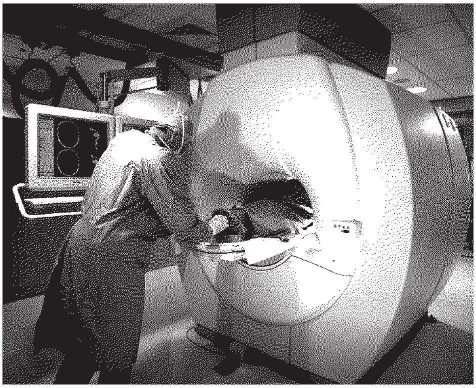

Figure 1.3. Example of an interventional procedure guided by MRI (neuro-imaging).

Interaction with materials and biological tissue

A number of dangers inherent to the use of strong magnetic fields, such as the danger of ferromagnetic objects being pulled into the magnet, were early recognized[47-49] and, since they might result in serious injury or death of the scanned individual[10,13,50,51], should be adequately controlled. Electrical equipment might also get damaged when it is exposed to strong magnetic fields, which might be lethal in the case of for example non-MR compatible cardiac pacemakers[52,53].

Three mechanisms have been proposed through which static magnetic fields (SMFs) can interact with biological tissue[7]:

(1) Mechanical effects: i.e. changes in orientation of dia- and paramagnetic molecules; (2) SMFs can exert Lorentz forces on moving ions which,

in general, induces Hall electric fields and associated currents; and (3) interactions of some chemical reactions that involve radicals with intermediate states.

The magnitude of the response of an object to an external magnetic field is proportionally to the strength of the magnetic field and the material's magnetic susceptibility (X). Diamagnetic materials ($-1.0 < X < 0$) are repelled from regions of strong fields. Most elements in the periodic table, including copper, silver, and gold, are diamagnetic. Paramagnetic materials ($0 < X < 0.01$), which include the vast majority of common materials including almost all living tissue, are often considered as non-magnetic. (Ferro)magnetic materials ($X >= 0.01$), such as iron and nickel, respond very strongly to an applied magnetic field.

Objects in a magnetic field experience forces that tend to move it in space, and torques which tend to align it with respect to the direction of the magnetic field. In biological situations where the magnetized body is small and the induced magnetization is similar in the whole object (isotropic) and the absolute value of the susceptibility is also small, any torques will be negligible[54].

In addition, when a cluster of macromolecules or cells are bound together with the same orientation to the magnetic field (crystalline or quasi-crystalline structure) the alignment torque is proportional to the number of molecules and the cluster volume (anisotropic susceptibility). This phenomenon seems to be the explanation why shape-dependent torques in tissues have been demonstrated in sickle cells in vitro[55], but not in vivo[56] nor in normal red cells.

Movement in strong magnetic fields[10] can induce electrical currents since, according to Maxwell's equation, any time-dependent magnetic field (dB_0/dt) will be accompanied by an electrical field (E) such that:

$$-\frac{\delta B}{\delta t} = \nabla x E$$

In a static electric field, the electric current density (J) in tissues is determined by $J=\sigma \cdot E$, where σ is the tissue's electrical conductivity and E is the electric field. If the tissue moves with a velocity (v) relative to the static field, there is an additional term for the current density, $J=\sigma(E + v \cdot B)$, where $v \cdot B$ is the motion-induced electric field.

The induced currents can have a variety of effects on the tissue, such as nerve stimulation observed during gradient switching in MRI[13] and transcranial magnetic stimulation (TMS)[57], and tissue heating related to the tissue's Specific Absorption Rate (SAR) which is a measure for the RF energy absorption as a result of the RF field in MRI[13].

Health Effects

Traditionally, the main focus of research on health effects and biological mechanisms of non-ionizing radiation has been on exposure to alternating electromagnetic fields; more specifically on extremely low frequency (ELF) fields and more recently, especially after the widespread use of mobile phone use, on radiofrequency (RF) electromagnetic fields[2,58-61]. Research on health effects of static magnetic fields, the focus of this thesis, has been rather limited[58,62].

Although effects of exposure to electromagnetic fields are typically expressed as complaints of poor concentration, impaired attention, and abnormal memory, similar to early warnings for neurotoxic exposure[63], acute health effects solely to the interaction of static magnetic fields and human are at present not well characterized. Soon after the introduction of MRI, a few small studies on patients scanned at 0.5 Tesla did not find any effects on the electroencephalogram (EEG)[64], nor was cognitive performance affected after being scanned at 0.5 or 1.5 T[64,65]. With the development of ultra-high magnetic fields several experimental studies were initiated, which either found no effects on cognition and cardiac function[66], or only a small, non-clinical, increase of systolic blood pressure[67] and decrease in short-term memory performance[68]. Furthermore, although a number of individuals have reported non-specific symptoms that they relate to low exposure to electromagnetic fields, no causal relation between "electromagnetic hypersensitivity (EHS)" and EMF exposure has been established[69].

Nevertheless, reported fatigue, dizziness, sleeplessness, headache, heart pain[70] and vertigo, metallic taste and nausea[71] have been related to presence in magnetic fields. The latter could be limited by the rate and frequency of motion within the field, suggesting that they may be related to induced currents from time-varying magnetic fields. Presumably, these symptoms are attributable to electric fields induced by movement within static magnetic fields. They can also artificially be induced by magnetic pulses in (repetitive) transcranial magnetic stimulation ((r)TMS) studies[17,72-75]. These induced currents can result[76] in direct depolarization of nerve and sensory cells, with experienced pain, peripheral nerve stimulation (PNS)[77-79] and magneto-phosphenes (although the emergence of phosphenes also depends on the attention of the subject[80]) as the most prominent effect[10,54]. Furthermore, diamagnetic anisotropy in the cupula might produce torque and deflection of its structure[13], thereby distorting ion-specific channels sufficiently to alter their function[81,82] which can result in vestibular effects. Vertigo might be more specifically caused by magneto-hydrodynamic forces acting on the endolymph of the semi-circular canals[54], which does not hamper hearing itself[83]. Studies in laboratory animals suggest that movement in static magnetic fields equal to or larger than 4T, but not at lower levels[84,85], is unpleasant[86-90]. In combination with switched gradient fields, rats' spatial discrimination learning was reduced at exposure to 2 T[91].

These responses were consistent with vestibular stimulation[92] and fairly similar to motion sickness[93,94], which is characterized by transient experiences of vertigo/dizziness, nystagmus, ataxia, and nausea[93]. Motion sickness is generally regarded as a normal and transient response to unfamiliar or unnatural motion stimuli[94,95], and involves complex central nervous system integration of various physiological and psychological cues[96], with a largely unknown aetiology. The almost[97] universally accepted explanation[94] is that it is triggered by a variance in the signals transmitted by the eyes, the vestibular system and the non-vestibular proprioceptors, and with what is expected on the basis of previous actions within the environment. The extent and severity of these symptoms are assumed to be directly related to the extent of mismatch.

Most vestibular syndromes involve both semicircular canal and otolith function[93], but symptoms (in different degrees of severity) of semicircular canal dysfunction are commonly reported as rotational vertigo, deviation of perceived straight-ahead, postural imbalance, spontaneous vestibular nystagmus, and nausea and vomiting, whereas otolith dysfunction are reported as symptoms of falls, linear motion or tilt suggestions, or postural orienting and balancing difficulties[98].

An important part of the vestibular system is the vestibule-ocular reflex (VOR)[99], which connects a set of extra-ocular eye muscles in response to information from the visual system, the otolith organs, the semi-circular canals, and other parts of the vestibular system. If the information to the VOR is at variance, this is expressed in gaze instability, which presumably aggravates the conflict between visual, vestibular, andproprioceptive inputs.

Long-term effects of exposure to static magnetic fields that have been studied are very few[6], but include fertility[100,101], pregnancy outcomes[100,102], and immune parameters[103]. No relations with MF-exposure were found in these studies.

Also, no long-term studies have been done exclusively for exposure to static magnetic fields and cancer risk. Studies in the aluminium industry, chloralkali industry[6] and among welders[104,105] focussed on chemical exposures, and static magnetic fields were only assessed to a lesser extent[6]. In 2002, the International Agency for Research on Cancer[106] concluded that there is inadequate evidence (group 3) in humans for the carcinogenicity of static electric or magnetic fields, and no relevant data were available from experimental animal studies.

If however, any relation exists between exposure to strong magnetic fields of MRI scanners and cancer it is likely to emerge in the upcoming decades since MRI has been widely used only since the 1980s, while it typically takes several decades between exposure and onset of solid malignant tumours[2].

ASSESSING NEUROBEHAVIORAL EFFECTS

Neurobehavioral test batteries can be used in research to detect acute, subtle, and reversible, changes in central nervous system function resulting from occupational and environmental exposures[107-110]. In general, these test batteries are used in experimental designs (in a controlled environment) where volunteers are exposed to different levels or duration of exposure. However, to study acute effects they have also been used in quasi-experimental designs in the workplace[110].

In general, these tests provide a powerful and relatively inexpensive tool to detect transient effects, but administering a complete test battery can be labour and time intensive[110]. Most batteries drew on already existing neuropsychological tests for their development[108], or were newly assembled from existing tests[111], depending on the research questions. However, many tests were initially developed for diagnostic purposes, but were nonetheless used for research[107-110]. In addition, it has been argued[112] to include tests assessing visual acuity and visual contrast sensitivity in neurobehavioral test batteries to avoid interpreting visual deficits as cognitive effects.

Many of these tests are prone to a practice, or learning, effect[113,114], and studies assessing repeated measurements with neurobehavioral tests indicated that, in general, this effect is strongest between the first and the second time a test is administered. The magnitude of the practice effect attenuates in following trials, and performance stabilizes after four trials for most tests[115-117]. Furthermore, data suggests that practice effects can still be present with weeks or months between two subsequent trials[118-121].

Finally, despite the wide-spread use of neuropsychological test batteries in clinical practice and research, the relation between test performance and functional capacity in daily living, occupational capacity, etcetera remains largely unknown, since it has not been explored frequently[63].

Aims and outline of this thesis

The results presented and discussed in this thesis are the result of a series of studies to understand and quantitatively assess effects of working in the vicinity of MRI magnets. More specifically, the objectives of the studies described in this thesis were:

(1) to assess type and frequency of health complaints as well as neurobehavioral effects that are experienced by engineers who assemble and test new magnetic resonance imaging systems, and

(2) to investigate the relation between neurobehavioral performance and exposure to stray fields generated by high, very high, and ultra-high MRI magnets.

Chapter two describes the first study, which assessed health complaints and neurobehavioral performance of employees at an MRI production company. In addition, mercury levels in urine were analyzed to investigate whether experiencing a metal taste in the vicinity of a magnet, a regularly occurring sensory complaint, might be due to amalgam release from dental fillings.

Chapter three describes an experimental pilot study among 20 company volunteers to assess whether neurobehavioral changes due to exposure to a static magnetic stray field from a 1.5 Tesla cylindrical MRI scanner could be measured using a collection of standard, non-computerized, neurobehavioral tests.

Chapter four evaluates recent studies assessing acute health effects and cognitive effects of exposure to static magnetic fields from high and ultra-high MRI scanners. More specifically, chapter four evaluates the results of the study described in chapter three in combination with results from a similar study by a different research group[67,68]. This combination resulted in the generation of a hypothesis for a study on exposure-response relations.

Chapter five describes a follow-up study with twenty company volunteers to assess relations between the magnitude of magnetic stray fields from 1.5 and 3.0 Tesla MRI magnets and effects on performance on a neurobehavioral test battery addressing a number of cognitive domains.

Chapter six deals with a study performed at the Sir Peter Mansfield MR-Centre at the University of Nottingham assessing neurobehavioral performance in the stray field of an ultra-high 7 Tesla MRI magnet. This study was done with twenty-seven naive volunteers recruited through ads at the university campus.

Chapter seven describes the main findings of this thesis and discusses a number of factors that might have influenced the results. In addition, it discusses results of a pooled analysis of results of the individual studies (details are presented in the Appendix). Furthermore, additional knowledge about biological mechanism of exposure to static magnetic stray fields is provided, and implications of results and provides directions for future research discussed.

Chapter 2

Exposure, health complaints and cognitive performance among employees of an MRI scanners manufacturing department.

Frank de Vocht
Hinkelien van Drooge
Hans Engels
Hans Kromhout

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ABSTRACT

Purpose: To assess sensory effects and other health complaints that are reported by system testers working near MRI magnets, realizing that it is believed that exposure up to 8 Tesla is safe for humans.

Materials and Methods: Levels of exposure to static magnetic fields (SMFs), movement speed during exposure, health complaints, and cognitive performance among employees in a MRI-manufacturing department and at a reference department have been analysed. Mercury concentrations in urine samples were determined to analyze whether they depend on exposure to SMFs.

Results: Average exposure of system testers was 25.9 mT/8 hours at a 1.0 T system and 40.4 mT/8 hours at a 1.5 T system. Vertigo, metal taste, and concentration problems were more reported among workers of MR-fabrication than in the reference department. Cognitive performance was tested outside the SMF, and no significant changes were detected.

Conclusion: This study suggests that any effects on cognitive functions are acute and transient and disappear rapidly after exposure has ended. All complaints, except for headaches, were more frequently reported by “fast movers” than by “slow movers”, and depended on field strength and duration of exposure. Mercury-levels in urine were not affected.

INTRODUCTION

It is widely believed[71,83] that exposure to static magnetic fields up to 2 T (International Commission on Non-Ionizing Radiation Protection (ICNIRP))[3] and to 8 T (Center for Devices and Radiological Health (CDRH) of the US Food and Drug Administration)[122] is safe for human beings. However, several transient sensory effects, including magnetophosphenes, dizziness, a metal taste, lack of concentration, headaches, and tiredness, have been reported at lower SMF strengths[10,71,123]. In rats, graded effects on behaviour were observed after exposure to 7 and 14 T[89], while other studies did not find any effects after exposure from 0.15 to 1.89 T[124-126]. In human volunteers, no clinical significant effects on human cognition were found during exposure to 8 T, although a small, not clinically meaningful, decrease in a test for recognition memory was noted[68]. Furthermore, systolic blood pressure was shown to increase with exposure to 8 T[67]. Other studies on human volunteers showed that during movement of the head and torso in the vicinity of a 1.5 T magnetic resonance imaging (MRI) magnet,eye-hand coordination and visual contrast sensitivity were affected (chapter 3). In a follow-up study it was shown that eye-hand coordination and processing of visual and auditive information was affected while moving one’s head in the vicinity of a 1.5 and a 3.0 T MRI magnet (chapter 5). Furthermore, it was shown that these effects depended on the strength of the magnetic field, which supports the concept of a field-dependent biological mechanism as suggested for sensory effects[54].

Following a concern from an MRI-manufacturing company regarding an increased prevalence of complaints of employees working in a department where MRI scanners were assembled and tested, we conducted a study assessing occupational exposure to magnetic fields, complaints, and cognitive performance. In addition, because workers also reported experiencing a metallic taste during exposure to magnetic fields and it was postulated that this could be due to a release of mercury from amalgam teeth fillings[127], we assessed mercury levels in urine samples of exposed employees and workers from the reference group. To our knowledge, this is the first study among employees manufacturing MRI-scanners focusing on the effects of occupational exposure to high SMFs.

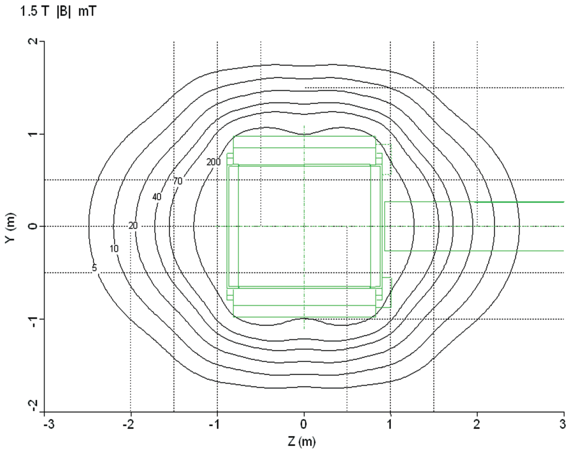

Figure 2.1. Top view of the spatial distribution of surrounding SMF B_0 of the 1.5-T magnet.

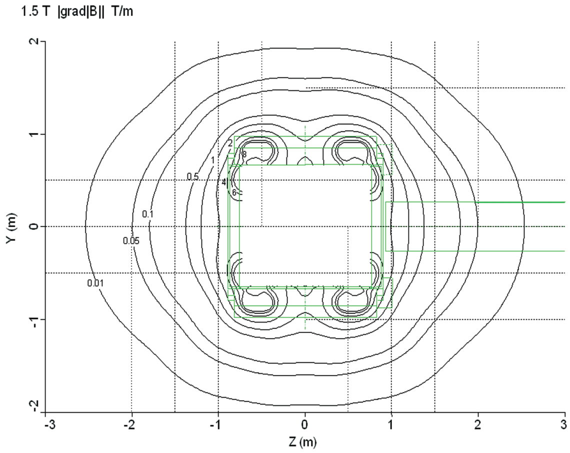

Figure 2.2. Top view of the distribution of the spatial gradient of B_0, |grad|B_0|| for the 1.5-T magnet.

MATERIALS AND METHODS

System

Exposure to SMFs was analyzed on five standard magnet-testing procedures, two at a system of 1.0 T and three at a 1.5 T system. Exposure was estimated by dividing the working area in several zones, along the magnetic field lines with equal magnetic field (MF) strength, ranging from 1 mT at the edge of the radiofrequency (RF) cage to 1.2 or

1.7 T in the bore of the magnet. The horizontal field lines were projected on the ground and divided the work area in five zones of 1-10 mT, 10-100 mT, 100-500 mT, 500 mT-1T and the area inside the bore of the magnet, respectively. Although there is also variation in MF strength in the vertical axis, we assumed that exposure at the height of the iso-center is an approximation of the average MF strength over the whole human body. The spatial distributions of the surrounding of the SMF (B_0) and of the spatial gradient of B_0 (dB/dx) are shown in Figures 2.1 and 2.2. Although the possible effects of exposure to different values of the spatial gradients of the SMF were not taken into account in this study, Figures 2.1 and 2.2 have been provided for future references to effects from exposure to the spatial gradients.

Population

Complaints were registered for all system testers working in the MRI systems manufacturing department (MRI) (n=18). As a reference population, employees from the same factory, but working in the X-ray cardiovascular systems department (X-ray) (n=20) were used. Both groups were comparable in terms of age distribution (mean 34.5 and 36.3 in the MRI and X-ray departments, respectively), years of education (15.3 and 14.6, respectively) and level of education.

Figure 2.3. Footage from two cameras placed in the RF cage and two inbore cameras during a standard system testing procedure.

Video system

Standard system testing procedures were recorded with four video cameras. Two cameras were placed in the RF cage aimed at the working area in the front and at the back of the magnet, and two other so-called *inbore* cameras were also aimed at these working areas but from inside the magnet bore (Fig. 2.3). Footage of all four cameras was simultaneously projected on a television set in one frame. Employees themselves switched the video recorders on when entering the RF cage and switched them off again when leaving the cage.

The duration employees were present in a certain area was based on the footage from the four cameras and was recorded precisely using a handheld computer with software package called The Observer (Noldus Technology, 1995). We used this package, developed for recording task durations, to precisely mark (based on four simultaneously projected video footages (Figure 2.3)) when an employee entered or left a marked area. Consequently, the software package estimated total time employees spent in each area and estimated time-weighted exposure to the SMF.

In addition, based on observations of two standard testing procedures (adjusting headcoils and placing of bottles and phantoms), the employees were divided into groups of fast and slow movers. First, based on the video footage, four scores were assigned to each employee:

(1) speed of movements in the RF cage
(2) number of movements in the RF cage
(3) speed of movements in the bore of the magnet
(4) number of movements in the bore of the magnet

Each measure was assigned an ordinal score of 1 (few or slow) to 5 (very much or very rapidly) and finally all scores were multiplied to derive an estimate of a worker's movement (Table 2.1). An analysis of variance showed that the way a worker moved in the RF cage was mainly a personal characteristic and did not differ significantly between the observed procedures (79% of the variability in the final scores was due to differences between individuals). The median value of the individual averaged scores was used to divide the exposed population into groups of slow and fast movers.

Table 2.1. Assigned Mover Group and Observation Scores (1-5) Based on Video Footage for Speed and Number of Movements for Two System Tests (Days) for Each Worker.

	System test 1 (day 1)					System test 2 (day 2)						Mover group
Employee	1	2	3	4	Score[a]	1	2	3	4	Score[a]	Mean[b]	
1	2	3	3	2	36	2	3	3	2	36	36	Slow
2	1	2	3	3	18	1	2	3	3	18	18	Slow
3	2	3	3	3	54	1	2	1	2	4	29	Slow
4	4	4	5	5	400	4	4	5	4	320	360	Fast
5	2	2	4	4	144	2	2	4	4	144	144	Fast
6	2	2	2	2	16	2	2	2	3	24	20	Slow
7	2	2	3	2	24	3	3	3	3	81	52.5	Fast
8	3	3	3	3	81	3	4	4	4	192	136.5	Fast
9	3	3	3	3	81	2	3	3	3	54	67.5	Fast
10	2	2	2	3	24	2	2	2	3	24	24	Slow
11	4	4	5	5	400	4	4	4	4	256	328	Fast
12	1	1	1	1	4	1	2	1	2	12	8	Slow
13	2	3	2	4	48	3	3	3	3	81	64.5	Fast
14	2	3	2	4	48	2	3	2	4	48	48	Slow
15	3	3	3	3	81	3	3	3	3	81	81	Fast
16	2	2	3	2	24	2	2	2	3	24	24	Slow
17	2	2	2	2	16	2	2	2	2	16	16	Slow
18	2	3	4	3	72	2	3	4	4	96	84	Fast
Between employee variance 79%												
Within employee variance 21%												

1 = assigned score for speed of movements in the RF-cage;
2 = score for number of movements in the RF-cage;
3 = score for speed of movements in the bore of the magnet;
4 = score for number of movements in the bore of the magnet.
[a] **Total-score calculated by multiplying 1,2,3, and 4;**
[b] **Average total-score.**

Questionnaire

During three consecutive weeks employees from MRI manufacturing and X-ray cardiovascular manufacturing departments completed a questionnaire after each working day. This questionnaire contained 15 different complaints, for which the employees had to indicate whether complaints occurred during the working day, were already present before the working day, or whether complaints from the day before lasted throughout the previous evening. The 15 evaluated complaints consisted of 11 complaints mentioned in the literature to originate from exposure to magnetic fields (headache, vertigo, muscle stimulation, concentration problems, tiredness, metal taste, suggestion of head ringing, irregular hearth rhythm, nausea, magneto-phosphenes and forgetfulness) as well as from reference complaints from studies on allergic complaints (running nose, sneezing, watery eyes and red and itchy skin).

In addition, employees were asked to estimate total time they had been working in the RF cage during a particular day, as well as more specific questions on activities performed with the start and end time of each activity.

Neurobehavioral tests

A neurobehavioral testing battery was administered to the employees working at MRI manufacturing and to the control group working at the X-ray cardiovascular department. Six computer-administered cognitive tests were selected from The Neurobehavioral Evaluation System (NES2) test battery to evaluate cognitive performance. This test battery were developed by Baker and Letz[128] based upon recommendations of the World Health Organization (WHO)[129], and adapted for use in The Netherlands by TNO Netherlands[130]. The selected tests evaluated motor-reaction (finger tapping), eye-hand coordination (sinusoide and saw shaped), attention (simple reaction time and changing attention), visuomotor speed (symbol/digit substitution test), and short-term memory (digit span [backwards]). The test battery was administered to subjects from MRI manufacturing on two days, before and directly after a working shift. On one day subjects were not exposed, or were exposed less than 10 minutes, to the magnetic field and on the second day they were exposed longer than 20 minutes. Individuals from the control group were tested on only one day, also before and directly after a working shift.

In addition, a small questionnaire was administered to all subjects about possible confounders (use of medication, alcohol consumption, tiredness, stress, and experience with computer games), as well as age, years of education, and level of education.

Long-term effects were evaluated by comparing the morning test scores of both groups, while semi-acute effects were evaluated by comparing the test scores in the morning with those after the working day. Furthermore, differences in test performance were also evaluated between fast and slow movers in the MRI-manufacturing department.

Determination of mercury in urine

To analyse whether exposure to strong magnetic fields increases release of mercury ions from amalgam fillings in the mouth, the concentration of mercury in urine samples of the MRI system testers and workers of the control group was determined.

The mercury concentration was determined in urine on Thursday morning for two consecutive weeks. Average concentrations in urine were compared for both groups and compared with a “normal value” of 3.5 µmol per mol creatinine. Mercury concentrations were determined with the Flow Inject Mercury-method (Perkin Elmer). Organically bound mercury is destructed with kalium permagnate and free anorganic mercury is reduced to metallic mercury with sodiumboriumhydroxide. Metallic mercury in turn is vaporized with a gas/liquid separator and the amount of mercury is determined with a mercury lamp.

In addition, all employees were asked to provide an estimate of their total time in the RF cage (on a daily basis) as well as the number of amalgam dental fillings.

Statistical analyses

Differences in the occurrence of complaints between departments, exposure levels, and duration of exposure were analyzed using the non-parametric Kruskal-Wallis test. In addition, trends between total number of complaints and exposure level or duration of exposure were assessed using linear regression techniques. Finally, changes in neurobehavioral test performance over a shift between exposure groups were analyzed using linear mixed effects models (chapter 3), which take into account natural heterogeneity in test performance between subjects in the study[131-133]. All analyses were conducted using SAS version 8.02 statistical software.

RESULTS

Exposure to the magnetic field

Exposure to SMF at the 1.0 T and 1.5 T magnets of system testers was estimated on the basis of video images (Table 2.2). Due to technical limitations it was only possible to obtain video footage during five standard activities of a system test and not during unexpected problems during the system tests. Estimated (arithmetic mean [AM]) 8-hour time-weighted average (TWA) exposure for technicians during system testing was 25.9 mT/8 hours at the 1.0 T scanner and 40.4 mT/8 hours at the 1.5 T system. However, differences between individuals were relatively large, with subjects exposed from only 4.2 mT/8 hours up to 91.0 mT/8 hours at the 1.0 T system and subjects exposed from 2.2 mT/8 hours up to 75.8 mT/8 hours at the 1.5 T system.

Table 2.2. Eight-Hour Time Weighted Average Exposure to Static Magnetic Fields in mT, Estimated from Video Images.

System (Tesla)	# Days	Time-weighted average exposure (milliTesla per day)			
		am	sd	Minimum	Maximum
1.0	8	25.9	28.5	4.2	91.0
1.5	11	40.4	23.3	2.2	75.8

am = arithmetic mean, sd = arithmetic standard deviation.

Table 2.3. Number (and Percentage) of Self-Reported Complaints in MRI Manufacturing Department and in Reference X-Ray-Cardiovascular Manufacturing Department.

	X-Ray cardiovascular		MRI manufacturing	
Complaint	complaints	subjects	complaints	subjects
Headache	12 (5%)	5 (10%)	6 (3%)	5 (27%)
Running nose	2 (1%)	2 (10%)	1 (0%)	1 (5%)
Sneezing	2 (1%)	1 (5%)	0	0
Watery eyes	0	0	0	0
Red, itchy skin	0	0	0	0
Vertigo	0	0	12 (6%)**	4 (22%)*
Muscle stimulation	0	0	0	0
Concentration problems	1 (0%)	1 (5%)	6 (3%)*	3 (16%)
Tiredness	11 (5%)	6 (30%)	12 (6%)	5 (27%)
Metal taste	0	0	22 (10%)**	2 (11%)
Suggestion of head ringing	7 (3%)	1 (5%)	11 (5%)	1 (6%)
Irregular heart rhythm	0	0	0	0
Nausea	0	0	0	0
Magnetophosphenes	0	0	0	0
Forgetfulness	2 (1%)	2 (10%)	1 (6%)	1 (6%)
N (persons)		20		18
Persons >1 complaint		12 (60%)		18 (67%)
N (complaints)	37 (15%)		70 (32%)	
N (days)	245		215	

*** *P*-value Kruskal-Wallis test <0.05; ** *P*-value Kruskal-Wallis test <0.01.**

Complaints

Results of the questionnaire are summarized in Tables 2.3-2.6. Vertigo, metal taste, and concentration complaints were significantly ($P_{\text{Kruskal-Wallis}} < 0.05$) more frequently reported in the MRI fabrication department than in the control X-ray departments. Furthermore, the number of individual workers reporting vertigo, but not concentration problems or metal taste, was significantly larger in the MRI fabrication department than in the X-ray department.

Table 2.4. Complaints Stratified by Magnetic Field Strength.

Complaint	0 Tesla	0.5 Tesla	1.0 Tesla	1.5 Tesla
Headache	0	1 (2%)	4 (7%)	1 (1%)
Vertigo	1 (5%)	0	3 (5%)	8 (9%)
Concentration problems	0	0	0	6 (6%)
Tiredness	2 (9%)	0	2 (3%)	8 (9%)
Metal taste	0	0	0	22 (23%)[a]
Suggestion of head ringing	0	0	0	11 (12%)[a]
Total	3 (14%)	1(2%)	9(16%)	56 (60%)[b]
Person days	22	41	58	94

[a] Significant different from 0 Tesla at the 5%-level (Kruskal-Wallis test).
[b] Increase of total complaints with magnetic field strength not statistically significant (*P*-value = 0.23).

In Table 2.4 the complaints are stratified by magnetic field strength in which the system testers worked. A statistically significant increase in the frequency of reported metal taste and suggestion of head ringing were found at 1.5 T. Furthermore, concentration problems, metal taste, and a suggestion of head ringing were only reported by system testers who worked at the 1.5 T system. Although an increase of "total complaints" with increasing magnetic field strength of the system can be perceived from Table 2.4, this trend did not reach statistical significance. Overall, the total number of complaints increased significantly with duration of exposure to SMFs ($P < 0.05$) (Table 2.5). For all specific complaints but concentration problems, Table 2.5 suggested an increase with prolonged duration of exposure, but did not reach statistical significance. Table 2.6 shows that, except for the occurrence of headaches and vertigo, all complaints were significantly ($P < 0.05$) more often reported by individuals classified as fast movers than by those classified as slow movers.

Table 2.5. Complaints Stratified by Duration of Presence in Magnetic Field.

	Duration [a]		
Complaint	0 Tesla	<=20 minutes	> 20 minutes
Headache	0	1(1%)	5(6%)
Vertigo	2(5%)	4(4%)	6(8%)
Concentration problems	1(3%)	2(2%)	3(4%)
Tiredness	2(5%)	1(1%)	9(12%)
Metal taste	1(3%)	15(15%) [b]	6(8%)
Suggestion of head ringing	1(3%)	8(8%)	2(3%)
Total	7(19%)	31(31%)	31(40%) [c]
Person days	37	101	77

[a] 20 minutes is the median of exposure duration (when magnetic field was present);
[b] Significantly different from 0 Tesla at the 5%-level (Kruskal-Wallis test);
[c] increase of total complaints with duration of exposure statistically significant at the 5%-level.

Table 2.6. Complaints Stratified by Moving Speed.

Complaint	Slow movers	Fast movers
Headache	4 (4%)	2 (2%)
Vertigo	4 (4%)	8 (8%)
Concentration problems	1 (1%)	5 (5%)*
Tiredness	2 (2%)	10 (10%)**
Metal taste	0	22 (21%)**
Suggestion of head ringing	0	11 (11%)**
Total	11 (10%)	58 (56%)
Persons	10	8
Days	111	104

*** *P*-value Kruskal-Wallis test <0.05;**
**** *P*-value Kruskal-Wallis test <0.01.**

Cognitive tests

Mean test scores of all cognitive tests for the morning and afternoon test sessions, as well as the *P*-values of the mixed effects models, are presented in Table 2.7. None of the possible confounders had a significant effect on test outcomes.

Table 2.7. Mean Test Scores (Standard Deviation) of the Morning and Afternoon Test Sessions for the Three Exposure Groups and P-values for the Differences in the Changes in Test Performance Over a Working Shift Between Exposure Groups.

	X-Ray		MRI low exposure		MRI high exposure		
Cognitive test	morning	afternoon	morning	afternoon	morning	afternoon	P-value*
Finger tapping dominant hand [a]	177 (29)	194 (24)	180 (24)	188 (32)	179 (23)	189 (29)	0.49
Finger tapping non-dominant hand [a]	165 (23)	177 (17)	168 (30)	170 (31)	162 (26)	168 (24)	0.06
Vinger tapping both [a]	228 (51)	252 (43)	197 (71)	224 (45)	218 (63)	232 (52)	0.69
Eye-hand coordination (sinusoide) [b]	1.53 (0.30)	1.33 (0.29)	1.48 (0.41)	1.27 (0.28)	1.33 (0.28)	1.22 (0.25)	0.48
Eye-hand coordination (saw) [b]	1.84 (0.34)	1.71 (0.23)	1.92 (0.28)	1.74 (0.20)	1.84 (0.22)	1.72 (0.17)	0.59
Simple reaction time [b]	237 (21)	235 (19)	231 (31)	237 (30)	236 (30)	242 (41)	0.47
Attention (square) [c]	276 (39)	261 (27)	274 (40)	258 (43)	258 (37)	260 (36)	0.18
Attention (arrow) [c]	407 (62)	373 (52)	385 (57)	377 (57)	377 (55)	379 (50)	0.20
Attention (square/arrow) [c]	628 (199)	498 (128)	612 (204)	492 (143)	520 (174)	444 (130)	0.61
Symbol digit [d]	2.22 (0.25)	2.02 (0.18)	2.25 (0.23)	2.11 (0.21)	2.18 (0.27)	2.06 (0.19)	0.44
Digit span (backwards) [e]	5.62 (1.19)	6.03 (1.36)	6.15 (1.28)	6.54 (1.28)	6.70 (1.02)	7.02 (1.20)	0.15

[a] Number of taps; [b] Number of pixels; [c] Milliseconds; [d] Seconds; [e] Number of remembered digits.
*** *P*-value of mixed effects models for the difference between morning and afternoon test scores.**

In all three exposure groups the test performance was enhanced in the afternoon test session compared to the morning session. No significant differences were found in the three motor-reaction tests between subjects in the reference X-ray, MRI low exposure, and MRI high exposure groups. Only motor-reaction with the non-dominant hand reached borderline significance (*P* = 0.06), with a smaller increase of finger taps over the working shift at the MRI department than at the reference department.

Hand-eye coordination tests were not negatively affected after being exposed to the SMF. Again, test performance was improved in afternoon sessions compared to morning sessions for all three groups. In the MRI department (high and low exposure) simple reaction time was slightly negatively affected during the work shift, although not statistically significant at the 5%-level, while it was not affected in the X-ray department. All attention tests (arrow, square and combined) were done better in the afternoon session than in the morning session, but no overall differences were found between departments. No differences were found between the morning and the afternoon test sessions for perception and coding ability (symbol digit and digit span tests) in all departments.

Mercury in urine

Mean mercury concentrations in the urine of subjects working in the X-ray or MRI departments are presented in Table 2.8. As shown, these concentrations range from 0.00 to 3.00 μmol Hg per mol creatinine. Overall, mean mercury concentrations were somewhat higher among subjects working at the reference X-ray department, although not statistically significant at the 5%-level, while the number of fillings was about the same (2.6 on average in MRI and 2.3 on average in X-ray).

Table 2.8. Mean Mercury in Morning Urine in μmol Hg Per Mol Creatinine.

Department	Mean	SD	Minimum	Maximum
MRI manufacturing				
Week 1	0.80	0.64	0.07	2.62
Week 2	0.89	0.76	0.00	3.00
X-Ray cardiovascular				
Week 1	1.30	0.67	0.20	2.30
Week 2	1.18	0.83	0.20	2.70

Duration of exposure to the magnetic field and concentration of mercury in urine at the MRI department were not related in the first week (correlation r=0.19), nor in the second week (r=0.13). However, a moderate correlation (r=0.60) was found between mercury in urine samples and number of fillings of employees.

DISCUSSION

Average exposure to the magnetic field was estimated from video footage to be at 34.3 mT/8 hours (range 2.2-91 mT/8 hours), which is well below the occupational exposure limit of 200 mT/8 hours[3]. However, especially during trouble shoot situations such as “spikes detection”, when an employee can be in the bore of the magnet for as long as one hour (based on information from the questionnaire), exposure is likely to exceed 200 mT/8 hours.

To estimate exposure, subjects had to manually switch on the video system when they entered the RF-cage and switch it off when leaving. This was not always done immediately, which resulted in partially missing tasks and minor under-estimation of true exposure. Furthermore, exposure to SMFs was estimated based on the time a subject was working in a specified “zone” and not on actual personal exposure measurements with a dosimeter. At the time of the study no personal dosimeters were existent that could be operated safely in an environment with such strong magnetic fields.

Dizziness, concentration problems, metal taste, and suggestions of head ringing were significantly more reported by exposed workers, with the latter two only being reported near 1.5 T MRI systems. An earlier study[71] found field-dependent sensory effects (nausea, vertigo and metal taste) at higher field strengths of 1.5 and 4.0 T. Our results suggested that these field-dependent sensory effects also occur at lower field strength, although the relatively small number of workers in this study (N = 38) precluded finding a statistically significant relation. The prevalence of reported headaches was, however, not related to the strength of the magnetic field in both studies. The total number of relevant complaints increased with duration of exposure to SMFs.

The system testers themselves estimated duration of the presence in the RF cage. Comparing their estimates with estimated duration from the video images showed that these estimates were relatively accurate (r=0.67) (data not shown). However, for individual situations, estimated presence in the RF cage could have been over- or underestimated, which could have resulted in non-differential misclassification of duration of exposure.

It has been postulated[25,134] that effects on cognitive functions and consequently experiencing several transient complaints is not caused by exposure to SMFs, but that moving in a static field activates highly sensitive sensory tissues by very weak electrical currents induced in tissue. Furthermore, sensations of nausea are probably the result of extraneous excitation of motion sensations by weak magneto-hydrodynamic forces in the semicircular canals of the inner ear and the resulting conflict between the position sensing apparatus of the vestibular and visual systems, or that these forces could arise from a diamagnetic anisotropy of the inner ear receptors. Our results show that employees from an MRI manufacturing department who moved more rapidly in the RF cage and consequently generated a stronger dynamic field, indeed reported more complaints than individuals who moved at a slower pace through the SMFs. Furthermore, moving speed and intensity was found to be to a large extent a personal characteristic, with a large between-subject and a small within-subject variance. This could explain why some individuals seem to be more sensitive to exposure to magnetic fields than others as suggested by the fact that although a two-fold higher percentage of complaints was found in the MRI department than in the X-ray departments (32% versus 15%, respectively), the number of individuals reporting complaints was similar (67% vs. 60%, respectively).

Cognitive tests only showed a small non-clinical negative effect of working in magnetic fields on finger tapping with the non-dominant hand. These findings are in line with results found in studies with volunteers at 8 T systems[68]. Effects on eye-hand coordination, visual contrast sensitivity and processing of visual and auditive information have been reported when measured in the direct vicinity of a 1.5 T (chapter 3 and 5) or 3.0 T (chapter 5) MRI magnet. Results in this study, where cognitive functions were tested outside the static magnetic field at least five minutes after exposure to the static magnetic fields had ended, suggest that effects on cognitive functions are acute and transient and are likely to disappear rapidly after exposure to static magnetic fields has ended.

No differences were found in the concentration of mercury in urine between exposed subjects and the reference group. These results are similar to those found in other studies[127,134] and show that metal taste experienced while present in a strong magnetic field is not caused by mercury that dissolves or vaporises from amalgam fillings. It has been postulated[83] that this effect is caused by small electrical currents on the surface of the tongue generated by moving in a magnetic field.

Although the effects reported in this study are of a subtle and transient nature, they can hamper employees during their work in these strong magnetic fields. Therefore, these results also suggest that from a practical viewpoint, employees working with MRI scanners should be instructed to consciously limit the speed with which they move while in strong magnetic fields.

CONCLUSION

In conclusion, this first study among employees exposed to SMFs during the manufacturing of MRI scanners has shown that especially fast moving workers, building and testing 1.5 T MRI systems for more than 20 minutes per shift, more often report typical complaints like vertigo, metal taste, head ringing and concentration problems. Computerized tests indicated no prolonged neurobehavioral effects after exposure to SMFs ended. The metallic taste could not be contributed to release of mercury from amalgam fillings. Future studies should focus on MRI systems operated at stronger SMFs (3 T) that are starting to replace systems evaluated in this study. Given the relative small sizes of occupationally exposed populations, studies with (larger) groups of volunteers should be considered. Finally, further studies will be necessary to determine the precise physiological basis of these effects.

3

Chapter 3

NEUROBEHAVIORAL EFFECTS AMONG SUBJECTS EXPOSED TO HIGH STATIC AND GRADIENT MAGNETIC FIELDS FROM A 1.5 TESLA MAGNETIC RESONANCE IMAGING SYSTEM

A CASE-CROSSOVER PILOT STUDY.

Frank de Vocht
Berna van Wendel de Joode
Hans Engels
Hans Kromhout

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ABSTRACT

The interactive use of magnetic resonance imaging (MRI) techniques is increasing in operating theatres. A study was performed on 17 male company volunteers to assess the neurobehavioral effects of exposure to magnetic fields from a 1.5 Tesla MRI system. The subjects' neurobehavioral performances on a neurobehavioral test battery were compared in four 1-hr sessions with and without exposure to magnetic fields, and with and without performing additional movements. Adverse effects were found for hand coordination (-4%, $P < 0.05$; Pursuit Aiming II) and near visual contrast sensitivity (-16% and –15%, $P < 0.10$; Vistech 6000™). The results from the remaining tests were inconclusive due to a strong learning effect. No additional effect from gradient fields was detected. The results indicate that working near a 1.5 Tesla MRI system may lead to neurobehavioral effects. Further research is recommended, especially in members of operating teams using interactive MRI systems.

INTRODUCTION

Magnetic resonance imaging (MRI) systems are starting to find their way into operating theatres, particularly in neurosurgery, where interactive MR systems can be used to help plan acute surgical corridors, confirm the accomplishment of operative objectives, and detect acute complications[135,136]. It is widely believed that exposure to static magnetic fields up to 2 Tesla (ICNIRP) and 8 Tesla (CDRH) is safe for human beings[3,71,83,122]. However, several sensory effects, such as magnetophosphenes, dizziness, a metal taste, lack of concentration, headaches, tiredness, and muscle stimulation have been reported at lower static magnetic fields[10,71,123]. The muscle stimulation can plausibly be ascribed to the activation of highly sensitive sensory tissues by very weak electrical currents induced in tissues by motion of the body through magnetic fields[10,54,123]. In a previous study in rats, graded effects on behaviour were observed after exposure to 7 or 14 Tesla[89]. Other studies have found no effects after exposure from 0.15 up to 1.89 Tesla[124-126].

Consequently, the increase in interactive use of MRI systems in operating theatres, and the exposure of operating teams to static and gradient magnetic fields, prompted us to study the neurobehavioral effects of exposure to these fields from a 1.5 Tesla magnet in 17 male company volunteers. The main objective of the study was to determine whether temporary effects on the human nervous system could be detected with the help of a neurobehavioral test battery during exposure to a 1.5 Tesla magnetic field.

METHODS

Study population

The initial study population consisted of 20 healthy male volunteers (38-57 years old, average age = 44 years) who worked in the departments of Magnetic Resonance Development and Magnetic Resonance Marketing at Philips Medical Systems, The Netherlands. The subjects' educational levels varied from B.Sc. to Ph.D. level.

Study design

During four sessions with and without exposure to the magnetic field of a cylindrical magnet of a 1.5 Tesla Philips *Intera* system, each subject performed six tests that evaluated cognitive-motor, cognitive, and sensory areas of the subjects' neurobehavioral system. A short description of all tests included in the test battery is provided in Table 3.1.

Table 3.1. Short description of the neurological testing battery.

Neurobehavioral test	Target area	Descriptions	Score
WHO-NCTB*			
Cognitive-motor			
Santa-Ana	Motor coordination, dexterity	180 degrees rotation of pegs in a peg-board, twice with the right and twice with the left hand (each time for 30 seconds)	Total number of correctly rotated pegs
Pursuit Aiming II	Precision	Placing dots in circles without touching the edge; as quickly as possible (60 sec.)	Precision: Number of correctly placed dots divided by total number of dots
	(hand coordination), Motor speed		Motor speed: Total number of dots
Cognitive			
Digit Span (backwards)	Verbal attention	Repetition (in reversed order) of random series of digits	Total number of correctly repeated series
Digit symbol substitution	Visuomotor speed	In 90 seconds as many symbols have to be paired with digits (from a key of pairs)	Total number of correctly paired symbols
Additional test			
STROOP	Visuoverbal interference	Report colors of color names printed in incongruously colored ink (randomly assigned)	Total number of good colour-word combinations
Sensory			
Vistech 6000™	Near visual contrast sensitivity	for 1.5, 3, 6, 12, and 18 cycles per degree - Recognizing the direction of lines for shrinking contrasts with one blinded eye	For each eye, highest score obtained twice is registered. Subsequently the average score of both eyes is calculated

(* World Health Organization Neurobehavioral Core Testing Battery)

Neurobehavioral tests were assembled from the WHO Neurobehavioral Core Test Battery[129,137,138] and extended with the STROOP test[138] and Vistech 6000™[139]. The tests were selected on the basis of two criteria: (1) ability to evaluate different neurobehavioral areas, and (2) ability to be performed in the magnetic field.

A case-crossover design[140] was used for this study. This is a variant of a case-control design[141], where case and control units are defined as different periods within the subject, which are as a result matched on individual factors[142]. It is important to use this type of design to eliminate error, since neurobehavioral test performance can be influenced by personal characteristics such as age, educational level, and intelligence. However, repeated application of neurobehavioral tests to the same subjects may lead to a "learning/practice effect", meaning that test performance improves the first few times as a result of the subject's experience. To minimize the learning effect in the current study, the volunteers performed all tests once prior to the actual tests under experimental conditions.

While the subjects performed the neurobehavioral tests, they sat or stood (Santa Ana dexterity test) at a table located as close to the bore of the magnet as possible. This location was comparable to the position that members of an operating crew would have when using MRI systems in operating theatres. As such, the subject's head was positioned in an area where the static field was in the order of 700 milliTesla (measured with a 3-axis Hall Teslameter (Metrolab Instruments SA)), and where the gradient of the magnetic field (dB_0/dx) was maximal.

The subjects performed tests under standardized conditions for a 1-hr period (the maximum allowed exposure time in a 1.5 Tesla magnetic field, calculated from the ICNIRP guideline on exposure to static magnetic fields[3]). Four different exposure conditions were used over a 4-week period:

(1) the magnet was switched off, and the subjects did not perform additional movements (week 1);
(2) the magnet was switched off, and the subjects performed additional movements (week 2);
(3) the magnet was switched on, and the subjects performed additional movements (week 3); and

(4) the magnet was switched on, and the subjects did not perform additional movements (week 4).

The magnet was energized overnight. At the start of each measurement session, the subjects were unaware of the magnet's status. The 1-hr measurement sessions consisted of repeated 4-min intervals of waiting (during a session without additional movements by the subjects), or making standardized movements (during a session including additional movements), immediately followed by a manual test of the neurobehavioral testing battery. The STROOP test was performed twice (once after 4 minutes and once after 55 minutes) to measure the possible effects of increased exposure. See Table 3.2 for a description of the entire test sequence.

The subjects' movements were described in a protocol and were meant to simulate a surgeon's movements during interventional procedures. The researcher (F.V.) who administered the test battery to the subjects also instructed subjects with regard to their movements. The movements consisted of putting an object into the bore of the magnet and taking it out, with a standardized time interval of 10s. In the presence of a magnetic field, such additional movements generate additional gradient fields.

Finally, personal characteristics, such as coffee and alcohol consumption, and feeling tired on the day of the measurement, were evaluated by a questionnaire.

Table 3.2. neurological test sequence in all exposure periods.

Sequence	Neurological test	Time (minutes)
	Start of measurement	0
1	STROOP 1st time	4
2	Pursuit Aiming II	12
3	Digit Memory Span	18
4	Digit/Symbol substition	24
5	Santa Ana dexterity	30
6	Vistech 6000™	40
7	STROOP 2nd time	55
	End of measurement	60

Exposure assessment

Three copper coils oriented in three dimensions (x, y and z) were placed on the volunteers' head during the experiments to characterize the actual intensity of the gradient fields generated by the subject's movements. Movement in the static magnetic field induced electric pulses in all of the copper coils. These were registered using the equation:

$$(dB/dt)_{x,y,z}=(V_{x,y,z})/A \qquad [1]$$

Where V is the electrical potential difference (Volt), A is the coil area (m^2), and dB/dt is in Tesla/s.

The intensity of the total gradient field was calculated using:

$$(\text{total gradient field})=\text{square root}(x^2+y^2+z^2) \qquad [2]$$

where x, y and z are the gradient fields generated in the x-, y- and z-directions, respectively.

Statistical analysis

Test results for all four measurement sessions were obtained from 17 of 20 subjects, and these were included in the statistical analyses. To account for the repeated-measures structure of the observations and enable the use of 68 (4 x 17) measurements in the analyses, the test results were analyzed with generalized linear mixed models (GLMMs)[131,132] using PROC MIXED in SAS v8.02™. GLMMs include both fixed and random factors in the model. Like a common regression model, the fixed effects provide estimates of the average test-scores of the subjects during the different measurement sessions.

Random effects account for the natural heterogeneity in the responses between subjects, and enable the analysis of repeated measurements on individuals. Random effects were assessed by the use of a compound symmetry (CS) covariance matrix, which assumes similar correlations between repeated measurements for all individuals. The use of the CS covariance matrix had no effect on the estimates for the fixed effects (i.e. effect of exposure). The residuals of the models were normally distributed. To minimize the learning effect, the volunteers performed all tests once prior to the actual tests under experimental conditions. We adjusted the statistical models for a residual learning effect by entering the order of the experiments in the models (model 1; Eq. [3]):

$$Y_{ijk} = (\mu + \alpha_i) + \beta_1 * \text{learning effect} + \beta_2 * \text{magnet} + \beta_3 * \text{movements} + \beta_4 * (\text{movements} * \text{magnet}) + \varepsilon_{ijk} \qquad [3]$$

where:
Y_{ijk} = test score of subject *i* with exposure condition k during test j.
$(\mu + \alpha_i)$ = test score for each subject *i* (random subject $\sim N(0,\sigma_b^2)$)
β_1*learning effect = adjustment for learning effect (fixed effect)
β_2*magnet = fixed effect of magnet turned on.
β_3*movements = fixed effect of additional movements.
β_4*(movements*magnet) = fixed effect of movements in the static field (gradient field).
ε_{ijk} = random error in test score ($\sim N(0,\sigma_w^2)$

Since no additional effects were seen in the movements or the gradient field, analyses were also performed using the reduced model (model 2; Eq. [4]):

$$Y_{ijk} = (\mu + \alpha_i) + \beta_1 * \text{ learning effect} + \beta_2 * \text{magnet} + \beta_{ijk} \qquad [4]$$

where:
Y_{ijk} = test score of subject *i* with exposure condition j during test *k*.
$(\mu + \alpha_i)$ = test score for each subject *i* (random subject $\sim N(0, \sigma_b^2)$)
β_1*learning effect = adjustment for learning effect (fixed effect)
β_2*magnet = fixed effect of magnet turned on.
β_{ijk} = random error in test score ($\sim N(0, \sigma_w^2)$

We assessed whether effects (β's) were significantly different from 0 at a 10% confidence level.

RESULTS

Since no additional effect of the presence or intensity (range = 7-50 Tesla/s) of the gradient fields was noted, only the results of model 2 are presented in Table 3.3. Overall, the results showed that a residual learning effect was prominent in four of the six tests. After adjustment for the learning effect, speed and precision (Pursuit Aiming II) and near visual contrast sensitivity (Vistech 6000™; 1.5 and 3.0 cycles per degree) were negatively influenced (–4% ($P < 0.05$), –16% and –15% ($P < 0.10$) respectively) when subjects were exposed to static and gradient fields generated by the 1.5 Tesla MRI magnet (Table 3.3).

Table 3.3. Neurobehavioral test battery scores and effects due to a 1.5 Tesla magnetic field.

Neurobehavioral test	mean[a] (se) test score[b] magnet off	mean[a] (se) test score[b] magnet on	effect magnetic field (se)	Relative effect magnetic field[c]
Digit Span (backwards)	7.3 (0.8)	7.2 (1.2)	-0.1 (1.4)	-0.0%
Digit Symbol	73.6 (2.0)	75.5 (2.8)	-0.1 (3.4)	+2.6%
STROOP (4 min)	55.5 (3.0)	57.6 (5.2)	+2.1 (6.0)	+3.8%
STROOP (50 min)	63.7 (2.8)	66.3 (2.6)	+2.6 (3.8)	+4.0%
Santa-Ana	68.1 (2.5)	67.6 (4.4)	-0.5 (5.1)	-0.7%
Pursuit Aiming II (Precision)	0.93 (0.0)[d]	0.90 (0.0)[d]	-0.03 (0.02)	-3.9%*
Pursuit Aiming II (Speed)	244.7 (6.9)	246.7 (6.7)	+2.0 (9.62)	+0.8%
VISTECH 6000™(mean of both eyes)				
(cycles per degree)				
1.5	77.6 (7.6)	64.9 (6.7)	-12.7 (10.1)	-16.5%**
3.0	133.8 (12.2)	113.2 (10.7)	-20.6 (16.2)	-15.4%**
6.0	146.2 (13.6)	138.0 (12.2)	-8.2 (18.3)	-5.6%
12.0	86.5 (9.6)	82.8 (8.8)	-3.7 (13.0)	-4.3%
18.0	36.0 (5.1)	33.4 (4.5)	-2.6 (6.8)	-7.2%

*** P<0.05 ; ** P<0.10**
[a] adjusted for "learning effect"; [c] % change estimated based on a mixed model;
[b] number of correct responses unless specified otherwise; [d] (total number of correct responses/ total number of responses).

DISCUSSION AND CONCLUSIONS

This experimental study is the first to show neurobehavioral effects measured by a test battery administered to individuals exposed to static and gradient magnetic fields from MRI systems. All of these tests in this study were performed on individuals during exposure to the static and gradient fields. This is in contrast to earlier studies in which neurobehavioral tests were done either immediately after exposure to an 8 Tesla magnetic field[66] or several days following NMR imaging of the brain with exposure to a 0.04 Tesla magnetic field, with a maximum field change of 0.12 Tesla/second[65]. Neither of these previous studies detected cognitive effects, which suggests that the field strength was too low[65], the effects disappeared rapidly after exposure, or the cognitive area remained unaffected by the exposure. The latter notion agrees with the current findings, as no adverse effects were detected for the two tests in the cognitive area. However, it is important to note that the applied cognitive tests were prone to a strong learning effect and therefore could not produce conclusive results.

Surprisingly, no additional effects from the gradient fields generated by the volunteers' movements were found. We hypothesize that the intensity of the additional movements in a static magnetic field of <=0.7 Tesla was not high enough to pick up a dose-response relation with the testing battery used in this study. However, it remains unclear whether the neurological effects measured can be solely explained by exposure to a static field, because the movements made by the subjects when they performed the neurobehavioral tests generated a gradient field as well. Likewise, operating crews performing interventional procedures are also exposed to the static and gradient fields of an MRI magnet simultaneously.

Most interventional MRI studies are currently performed with open MRI systems at a field strength <= 0.6 T. However, the current experiments were performed in an magnetic field of the cylindrical magnet of a 1.5 Tesla Philips *Intera* system because: (1) previous studies have described operations performed with cylindrical 1.5 Tesla systems[136,143]; (2) it is expected that, given their improved imaging capabilities, higher field-strength MRI scanners will be used for interventional applications in the near future; and (3) neurobehavioral effects are expected to be more pronounced at higher magnetic field strengths.

All of the volunteers selected for this study were accustomed to working near (high static) magnetic fields. Consequently, the results were not influenced by the psychological effects of being in such an environment for the first time, as was noted in a previous study involving a sample of the general population[10,71]. Furthermore, all volunteers were interviewed immediately following the test. One of the questions asked was, "Was the magnetic field in your opinion on or off?" With the magnet turned on, 61% of the volunteers did not experience any effects, and thought the magnet was off. With additional movements in the gradient field, 35% of the subjects still did not experience any effects of exposure. This indicates that any trend in test performance was probably not caused by familiarity with an MRI system.

The current study shows that neurobehavioral tests can be used to assess the effects of working in an environment with high static and gradient magnetic field. However, the results of the Santa Ana, Digit Span, Digit Symbol substitution and STROOP tests were strongly influenced by the learning effect, which made them unsuitable for use in evaluating the study objectives. Another drawback of the neurobehavioral test performances is that they cannot be related to a quantitative estimation of impairment on an actual surgeon’s performance during interventional procedures. It remains unclear how a reduction of 4% in speed and precision (as measured by Pursuit Aiming II), and a 15% and 16% reduction in near visual contrast sensitivity will affect a surgeons’ performance. On the other hand, it is obvious that changes in neurobehavioral functions can have important implications for how well a surgeon performs his or her job.

In conclusion, the current results indicate that working near a 1.5 Tesla MRI system may lead to measurable (probably temporary) neurobehavioral effects, even after a short exposure. Since these effects could influence the performance of an operating crew during interventional procedures, further research is recommended to reproduce these findings, especially in members of operating teams using interactive MRI systems, with even stronger magnets, in operating theatre.

Chapter 4

STATIC MAGNETIC FIELD EFFECTS ON HUMAN SUBJECTS RELATED TO MAGNETIC RESONANCE IMAGING SYSTEMS.

Donald W. Chakeres
Frank de Vocht

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ABSTRACT

Goal: This paper reviews recent studies evaluating human subjects for physiologic or neuro-cognitive function adverse effects resulting from exposure to static magnetic fields of magnetic resonance imaging systems.

Material and Methods: The results of three studies are summarized. Two studies evaluated expose to a maximum of 8 Tesla (T). The first series studied 25 normal human subjects' sequential vital signs (heart rate, blood pressure, blood oxygenation, core temperature, ECG, respiratory rate) measured at different magnetic field strengths to a maximum of 8 T. A second series of 25 subjects were studied at 0.05 and 8 T (out and in the bore of the magnet), performing 12 different standardized neuro-psychological tests and auditory- motor reaction times. The subjects' comments were recorded immediately following the study and after a three-month interval. The third study contained 17 subjects, placed near the bore of a 1.5 T magnet, and it used six different cognitive, cognitive-motor, or sensory tests.

Results: There were no clinically significant changes in the subjects' physiologic measurements at 8 T. There was a slight increase in the systolic blood pressure with increasing magnetic field strength. There did not appear to be any adverse effect on the cognitive performance of the subjects at 8 T. A few subjects commented at the time of initial exposure on dizziness, metallic taste in the mouth, or discomfort related to the measurement instruments or the head coil. There were no adverse comments at 3 months. The 1.5 T study had two of the four neuro-behavioral domains exhibiting adverse effects (sensory and cognitive-motor).

Conclusions: These studies did not demonstrate any clinically relevant adverse effects on neuro-cognitive testing or vital sign changes. One short-term memory, one sensory and one cognitive-motor test demonstrated adverse effects, but the significance is not clear.

INTRODUCTION

Magnetic resonance imaging (MRI) has become a very important standard medical imaging modality. Hundreds of millions of patient examinations have been safely completed using MR. MRI has many advantages, including: no ionizing radiation, extreme imaging flexibility, high patient acceptance, evaluation capability of both anatomic and physiologic parameters, acquisition of unique clinical information, and it is non-invasive. MRI requires a static magnetic field, transient magnetic field gradients, and a radio frequency (RF) transmitter and receiver system. There have been very few safety problems reported with MRI systems relative to the huge number of exams that have been completed. The most commonly reported problem is claustrophobia and patient anxiety related to the confined space within the magnet. The most common significant safety complication is related to RF burns from localized heating. Much less common, but potentially life threatening safety problems can be caused by magnetic projectiles pulled into the magnet, torque on metallic foreign bodies or implants, and magnetic or RF interference with medical devices. A few MRI fatalities have been reported[144,145].

Safety problems related solely to the interaction of static magnetic fields and humans (with no metallic hardware involved) are much less common, and are presently not well characterized[64-66]. There are many studies showing interaction between medical equipment and a static magnetic field[146,147]. In the past, the primary safety concerns have focused on patients, since technologists and physicians are only transiently near the magnet. With the advent of interventional MRI, interventional procedures are completed in or adjacent to the magnet, and the potential effects of acute and/or long-term exposure to the medical staff are much greater[40,148,149]. In this case, the potential exists for medical staff to actually be inside the magnetic field for hours for each procedure and thus potentially for significant period of time per year. If interventional MRI studies become more common[40], then additional extended high-field safety exposure studies are advisable.

This paper reviews a number of recent papers related to the potential for adverse effects resulting from the static magnetic fields associated with MRI systems on human volunteers evaluated with systematic testing in the magnetic field (chapter 3)[67,68].

MATERIALS, METHODS AND RESULTS

MRI Systems

All studies were done under investigational review board supervision and with informed consent. All of the subjects were normal volunteers. The subject's vital sign measurements were normal and they had no significant known medical problems that would increase their risk of exposure or would affect their performance on neuro-behavioral tests. The 1.5T study volunteers were also employees of the MRI manufacturer. Two of the studies were made using an ultra-high-field research prototype MRI 8 Tesla (T) system (Abingdon, UK)[67,68].

The 8 T study used a *Magnex*-General Electric 80 cm bore magnet. An asymmetric gradient coil and a 32 cm long transverse electromagnetic RF coil were used, although they were not operational for these studies since there was no imaging involved. The other study utilized the magnet of a routine clinical 1.5 T Philips *Intera* system with the gradient coils removed (chapter 3). In all of the 8 T studies, the magnet was not ramped down. The subject was placed at various field strength locations (relative to the head) and instructed not to move. The system utilized a movable cantilevered table.

The 1.5 T subjects were seated as close to the bore of the magnet as possible. The maximum local magnetic field strength at this location was approximately 700 mT. Some of the 1.5T studies were done with the field on and others with the field off. The subjects were not aware of the magnet's field status. Furthermore, measurements were done once with motion and once without motion, both when the magnet was turned on and when it was turned off.

Subject comments related to magnetic field exposures up to 8 T

The 8 T subjects were asked to make any comments related to their exposure immediately following the study and after a 3-month interval. No subject complained of any serious adverse effect. A number of subjects commented on transient metallic taste in the mouth, dizziness, or vertigo associated with entering or leaving the bore of the magnet. The subjects on the table were intentionally moved slowly through this region in order to minimize potential symptoms. It was not possible to avoid all subject symptoms. Other subject comments related to the cold temperature, the small bore, or the uncomfortable vital sign monitoring equipment. There were no comments related to magnetophosphenes (transient light flashes) in this group. At 3 months there were no reported delayed problems.

At 1.5 T, there were no differences in the frequency and type of complaints when the magnet was turned on and when it was turned off.

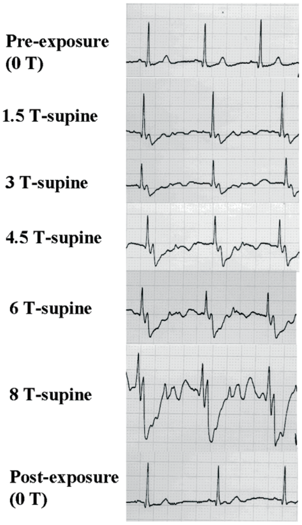

Figure 4.1. Changes in the electrocardiogram related to magnetic field strength.
This figure demonstrates the ECG recording of a single individual pre-exposure (0 T), 8, 6, 4.5, 3, 1.5 T and post- exposure (0 T). Note the distortions of the ECG with increasing magnetic field strengths. The ECG returns to normal after the magnetic exposure. The field strengths are related to the head locations.

Sequential vital sign evaluation related to field strength or neuro-cognitive testing stress at 8 T

One of the 8 T studies focused on potential physiologic changes related to static magnetic field exposure[67]. Control measurements of the study included measurements made in both the sitting and supine position out of the magnet, in the control room out of the magnetic field. The other control was an identical series of supine measurements made outside of the field.

The next 8 T study focused on neuro-cognitive performance of the subjects, and sequential vital sign measurements were made in a similar fashion. The sequential measurements included temperature of the external auditory canal, respiratory rate, systolic blood pressure, diastolic blood pressure, pulse rate, finger oxygenation level, oral sublingual fibre optic temperature, and electrocardiogram (ECG).

The external auditory canal temperature and the respiratory rate were only measured out of the magnetic field. Both sitting and supine measurements were made. The dedicated physiologic study made measurements every 5 min at multiple decreasing field strengths at the head corresponding to strengths of 8, 6, 4.5, 3, 1.5, and 0 T.

The order of whether the subject was first evaluated “out” of the magnet for the series of measurements or first “in” was randomized. The measurement data was statistically analyzed by a repeated measures analysis of variance to determine the significance of the different potential effects. A cardiologist reviewed the ECG data for changes.

The results (Figure 4.1) showed that there were statistically significant changes in many of the physiologic parameters measured in the supine compared to the sitting position, including heart rate and blood pressure changes. The only physiologic parameter that statically correlated with field strength exposure was a small, but measurable change in systolic blood pressure. The systolic blood pressure was slightly higher at higher field strengths. The maximum change for 8 T was approximately 3.6 mm Hg. This actual measured change was only one-half the systolic blood pressure change observed when the subject moved from a supine to a sitting position when not exposed to any field. There were characteristic changes of the ECG with magneto-hydrodynamic effects[150]; however, there were no significant changes of the pre- and post-exposure ECGs. Some transient episodes of sinus tachycardia were measured for the subjects undergoing neuro-cognitive testing. These resolved quickly and directly correlated to the stress levels some subjects felt when taking the more difficult verbal testing segments (for example, longer number series to recall). There were no symptomatic physiologic changes recorded at any time.

Cognitive and motor function testing at 8 T

This study evaluated subjects at 0.05 and 8 T[68], performing 11 different standardized neuro-psychological measures and auditory-motor reaction times measuring the short-term memory, working memory and the attention cognitive domains (i.e. tasks evaluating the same cognitive function of the brain)[151]. Physiologic monitoring was completed throughout the exam. The examinations were done with the head centred at either 8 T or at 0.05 T, the effective field present at the door of the system room. Efforts were made at the 0.05 T location to simulate the 8 T magnet room environment as closely as possible. The order of the testing was random as to whether the tests were first made "in" or "out" of the magnet. One investigator communicated via a microphone in the control room with the patient. The patient wore auditory headphones connected by tubing to speakers outside of the MRI room. A second investigator communicated with the subject and stood next to them to record their responses. A series of 11 standardized neuro-cognitive tests evaluated learning, retention, recognition, fluency, digit span forward, digit span backwards, and number-letter trials. There was also an auditory-motor reaction time test in which a computer program generated three tones, and upon hearing the third tone, the subject squeezed a hand-held button to test reaction time. The reaction times and number of errors (premature reaction times) were recorded. All data were statistically evaluated using standard neuro-cognitive software (Statistical Package for the Social Sciences version 10). A series of univariate comparison (t-test for correlated means) was used.

The results showed that there were no clinically significant (statistically significant at the 5% level and a change that could be significant in terms of anticipated normal performance) neuro-cognitive effects on the subjects resulting from exposure to the 8 T magnetic field. In fact, more testing measures were higher when the subjects were inside the magnet compared to the scores recorded outside the field, but this was not statistically significant ($P < 0.05$). The word recognition test was the only test that had any statistically significant findings, although they were not clinically significant since the actual values were very close to each other. Almost all of the subjects had correct responses for this segment of the exams.

Cognitive and motor function testing at 1.5 T

In this study, 17 company volunteers were seated in the vicinity of a 1.5 Tesla magnet, two times with the magnet turned on and two times with the magnet turned off (chapter 3). In addition, standardized additional movements of the head and torso (aimed at mimicking a surgeon during an interventional procedure) were done once when the magnet was on and once when it was off to analyze any additional effects of moving in the static MF. Subjects were unaware of the status of the magnet.

In a 1-hour period, six different cognitive tests were done, evaluating the cognitive, the cognitive-motor, and the sensory domains. Results were analyzed statistically using generalized linear mixed models to account for the within-subject repeated measurements.

The results showed that eye-hand coordination and near-visual contrast sensitivity were negatively influenced by exposure to the static magnetic field. The mean reduction in test performance was −4% for eye-hand coordination and −16% for visual contrast sensitivity. Dexterity, visuomotor speed, visuoverbal interference, and verbal attention were not affected.

DISCUSSION

No clear hypothesis has been proposed that would account for serious health effects on biological systems when exposed to static magnetic fields. Most biological tissues are weakly magnetic and diamagnetic. In contrast to ionizing radiation, where risk was recognized early, there is little data to demonstrate any serious health risks related to static magnetic field exposure of humans. No adverse effects have been seen on small animals and cell cultures, even with extended intervals of exposure to very strong static magnetic fields up to 10 T[152,153].

Most of the safety problems related to MRI have not been related to a direct biological effect of the magnetic field on human subjects or the medical staff. Instead, non-field problems related to RF heat deposition are much more common[154,155]. The better-understood health risks of magnetic fields relate to magnetic projectiles, medical hardware interference (cardiac pacemakers or neuro-stimulators), or torque on metal structures such as aneurysm clips[144]. All of these interactions have been associated with fatalities.

There are no good long-term high-field exposure studies to confirm there is no significant or long-term biologic injury to humans. Also, due to the long latency time between exposure and the manifestation of solid tumours, any excess risk for malignant tumours caused by exposure to high magnetic fields was not likely to show up in epidemiological studies previously, given that 1.5T clinical MRI-systems were the state-of-the-art only 2 decades ago and several 3 and 4T experimental human systems were only introduced and put into research use 15 years ago[156,157].

There is one complicating safety issue though, and that is that though the magnetic field may be static, when an individual moves through the field it is not homogenous. As a result of this, patients entering and leaving the magnet, as well as the medical staff moving around the magnet, are exposed to varying magnetic fields. This movement is associated with the production of secondary induced electrical currents. For interventional MRI procedures, the medical staff moves around extensively in the field. Organs and liquid tissues also move within the field, even if the patient or medical staff is stationary. For these reasons, it is important to take motion variables into account when analyzing static magnetic field effects.

In general, for most magnetic designs, particularly standard cylindrical magnets, the highest static magnetic field gradient is centred in the bore of the magnet. This is the location where most individuals report symptoms related to static magnetic fields. It is also the location exhibiting the greatest force on magnetic materials. The magnetic field strength and the magnet design (for example, self-shielded magnets or external shielding), influence the actual configuration of the static magnetic field and all may be important factors in human studies. Human exposure to the local magnetic field gradients will vary widely. For example, a patient having a brain MRI will have their head in the centre of the magnet, where the field is much more homogeneous. In contrast, a patient having an MRI of the foot may have their head positioned at the bore of the magnet. Also, certain tests require engineers to work in the bore of the magnet, while others require them (or operating teams during interventional procedures) to work outside, but in the vicinity of, the MRI magnet. It is important to characterize the relationship of the subject to the static field and the motion they are undertaking since the field exposure varies with these differences.

The biological effects that a subject tends to recognize are not usually related solely to exposure to a static magnetic field, but rather to the subject's motion across a magnetic gradient. Subjects in the centre of the 8 T magnetic field rarely have any comment on any symptoms perceived even when moving at this location, though symptoms are sometimes perceived while moving in or out of the magnetic field. One biologic marker of movement through a static magnetic field gradient may include a transient metallic taste in the mouth, probably due to electrolysis of metallic fillings in the teeth induced from local current generation (since moving a conductor through a magnetic field will induce an electrical current). It is possible that direct neural alterations similar to visual stimuli could occur in the tongue, but less likely since electrolysis is anticipated. Transient sensations of amorphous “lights” in the eyes, called magneto-phosphenes, have also been reported. This effect is similar to that observed when squeezing a closed eye tightly. This transient finding is uncommon and is clearly not harmful to the subject, but is something that should be avoided during interventional procedures. This phenomenon is most likely caused by the diamagnetism of the retinal rods, which when rotated experience a slight torque that is responsible for this illusory stimulation[47].

Perhaps the most distressing symptom for most subjects related to high magnetic field exposure (usually above 2T) is a feeling of dizziness or vertigo when moving through the field. This has been postulated to arise from magneto-hydrodynamic forces within the inner ear. Motion of the head within a magnetic field gives rise to magneto-hydrodynamic forces that are misinterpreted by the brain arising from an angular rotation. This conflicts with the information received from the visual system, giving rise to similar effects as those found in travel sickness[25]. This only rarely leads to nausea or vomiting, but it can be transiently distressing or disorienting to some subjects. Most intervals of dizziness are very brief, in the range of 1 min or less, but any symptom producing a feeling of disequilibrium is usually reported as adverse by subjects. Perceived dizziness or vertigo only rarely would lead to an interruption or cancellation of an examination. Individuals moving around in the proximity of very high-field magnets can develop these symptoms without actually entering the magnet and this can consequently interfere with the work of technicians and physicians. More subtle effects on balance and motor control could adversely affect motor and cognitive performance. This could lead to potentially significant alteration of complicated procedures by a surgeon during interventional procedures in the operating room. Although the neuro-behavioural tests used in these studies cannot be directly related to a reduction in actual performance of surgeons (chapter 3), significant reductions were found when exposed to the magnetic fields of a 1.5T MRI magnet. It is anticipated that in the near future the magnetic field strengths for human applications will increase, as well as the number of interventional procedures[25], and to our knowledge it is still unclear whether there is a dose-response relationship between magnetic field strength and balance, motor control or visual contrast sensitivity.

Changes in the ECG are not apparent to the subject. There did not appear to be any permanent change in the cardiac performance related to field exposure, though there was a minor insignificant increase in blood pressure. No arrhythmias were recorded. Both of these effects relate to magneto-hydrodynamic effects, in which blood moving perpendicular to the magnetic field generates a small current[150]. This is most prominent in a horizontal bore superconducting magnetic in the arch of the aorta. The descending and ascending aortas are more parallel to the magnetic field and therefore generate less current. These induced currents produce small electrical potentials that are superimposed on the routine ECG, generating an amorphous pulse, primarily during systole (Fig. 4.1). Other smaller flows and flow-related effects can also influence the ECG, and, in general, the higher the field, the greater the observed ECG distortion. Despite being measurable, this change in the ECG does not appear to have any clinical significance, and is probably just an artefact. Detailed studies of patients with conduction disorders at high field have not been completed.

The only physiologic parameter that was found to be minimally altered statistically significant by high-field exposure was a change in measured systolic blood pressure. This observed increase in systolic blood pressure is consistent with a hemodynamic compensatory mechanism to counteract the magneto-hydrodynamic slowing of the blood flow. In this case, the current generation produces its own magnetic field that is counter to the local magnetic field, producing increased flow resistance. In theory, at field strengths of 8 T there could be a reduction in blood volume flow rate of –3%[158]. A change in the systolic blood flow in that range is recorded with a compensatory increase in the blood pressure.

Two of the studies evaluated neuro-cognitive function at 8 and 1.5 T, respectively. The neuro-cognitive tests used evaluated a number of different parameters, including short-term memory, working memory, and attention in the 8 T study and psychomotor, short-term memory, attention, and visual contrast sensitivity in the 1.5 T study (Table 4.1). Of these, only short-term memory and attention were evaluated in both studies. Only in the 8 T study was a small negative effect on short-term memory noted. In addition, no influence on working memory was found in the 8 T study, but this was not analyzed in the 1.5 T study. These test results suggest that these cognitive functions are not very sensitive to magnetic field effects, even when the field is very high. This finding confirms results from older studies[65], though the reason for this finding is unclear. It may be that the dimensional scale of the cellular components associated with cognitive functions is miniscule or is based on chemical alterations; if this is the case, a magnetic field interaction effect might not cause an alteration in local neural function.

Table 4.1. Comparison of neurobehavioral test results 8 T and 1.5 T studies.

	De Vocht et al., 2003		Chakeres et al., 2003b	
Subjects	17		25	
Measurements	68		50	
Exposure assessment				
MRI system	0 + 1.5 Tesla		0.05 + 8.0 Tesla	
Area	Vicinity of magnet		Inside and outside of bore	
Exposure	<700 mT		0.05 + 8.0 Tesla	
Movement in MF	yes		No	
Tests in MF	yes		Yes	
Neurobehavioral test	# tests	#positive tests	# tests	#positive tests
Psychomotor	2	1	-	-
Short-term memory	1	0	3	1
Attention	2	0	3	0
Visuo-sensory	1	1	-	-
Working memory	-	-	2	0

Adverse changes in performance were observed in two domains in the 1.5 T study, but these were not tested in the 8 T studies. Performance in the eye-hand coordination tests was reduced on average by 4% and near-visual contrast sensitivity by 16%. An additional effect of the head and torso movements could not be demonstrated in this study, but it was hypothesized that this was caused by the fact that either the movement intensity was too low or too much movements was generated during test performance in all four testing periods to be able to separate any additional effects from movements only.

In the 1.5T study, motor coordination and eye-hand coordination were evaluated with and without significant movements of the head and torso in the magnetic field. In the 8 T study, an auditory- motor response was measured. The possibilities for motion testing within the magnet bore are very limited, so an ideal test to evaluate movement may not have been utilized. However, for evaluating the effects of exposure to magnetic fields on personnel working in the vicinity of the magnet, it is not necessary to measure inside the magnet bore, making motion testing relatively easy. At present, it is not possible to directly link test performance to work performance "in the field". Furthermore, during motion testing volunteers move in the magnetic field and consequently create an additional exposure to dynamic magnetic fields. Determining whether any motion effects are related to the static magnetic field or to the dynamic magnetic field will be complicated, although the latter is generally assumed.

CONCLUSION

There are no findings to suggest any permanent adverse effect on human subjects when exposed to static magnetic fields in strengths of up to 8 T. There is no evidence of any clinically relevant alteration in human neuro-cognitive function related to static magnetic field exposure. Results suggest that the cognitive-motor (eye-hand coordination) and the sensory (near visual contrast sensitivity) are negatively influenced by exposure to magnetic fields as low as 700 mT. Although these effects are undesirable in interventional MRI procedures, it is not clear how these transient effects relate to actual performance in a clinical setting. The risks related to the interaction of a static magnetic field and magnetic or electrical hardware are much greater than the apparent biological interaction risks to human subjects alone.

Chapter 5

ACUTE NEUROBEHAVIORAL EFFECTS OF EXPOSURE TO STATIC MAGNETIC FIELDS: ANALYSES OF EXPOSURE-RESPONSE RELATIONS.

Frank de Vocht
Tobias Stevens
Berna van Wendel de Joode
Hans Engels
Hans Kromhout

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ABSTRACT

Purpose: To assessed exposure-response relations between exposure to magnetic fields and neurobehavioral effects. Materials and Methods: Twenty company volunteers completed a neurobehavioral test battery after moving their heads with the magnetic field absent, and while moving their heads in the inhomogeneous stray fields of 1.5 and of 3.0 T MRI magnets.

Results: The value of the stray fields at the position of the head of the volunteer was estimated to be 0.6T and 1.0T at the 1.5T and 3.0T systems, respectively.

Exposure-response relations were found for visual (-2.1% / 100 mT) and auditory (-1.0% / 100 mT) working memory, eye-hand coordination speed (-1.0% / 100 mT) and visual tracking tasks (-3.1% / 100 mT). Eye-hand precision, scanning speed, and visual contrast sensitivity were apparently not influenced by the magnetic field strength.

Conclusion: Additional research should focus on the potential side effects of interventional MR procedures because of the exposure to strong magnetic fields of these systems.

INTRODUCTION

Recent trends in diagnostic MRI procedures include a more extensive use of interventional procedures[40,159,160] and the use of stronger magnets[25]. Although these procedures have certain advantages, they also expose the operating teams to high static, inhomogeneous magnetic fields generated by these systems because the operating teams operate in the stray field of the magnet. Although it has been shown that reports of field-induced sensory effects in the vicinity of MRI magnets can be elicited even when the magnet is ramped down[71], the incidence of reports of sensations of nausea, vertigo, metallic taste and magneto-phosphenes (brief flashing lights) increases with the magnetic field strength[71,161]. This supports the concept of field-dependent sensory effects[54]. In addition, a recent study suggested that exposure to the magnetic fields generated by a 1.5 T MRI magnet temporarily affects the subject's performance in the psychomotor and the visuo-sensory domains, but not in the short-term memory and attention domain (chapter 3). The latter finding was supported by a study with an 8 T magnetic field[68]. The affected performance in the psychomotor and visuosensory domains could potentially influence work of operating personnel performing interventional procedures (chapter 4).

In this study we evaluated exposure-response relations between exposure to magnetic fields and neurobehavioral effects. The results provide additional evidence for a causal relation between exposure and effects.

MATERIALS AND METHODS

Study Population

Twenty healthy male volunteers (age = 25 to 59: mean = 42 years) were selected from the business unit of a company that developed and manufactured MRI magnets. The volunteers were familiar with strong magnetic fields and MRI scanners, but did not necessarily work with the scanners on a daily basis. Their education varied from secondary vocational education (N = 5) to B.Sc. (N = 12) and Ph.D. (N = 3) levels.

Exposure Assessment

All subjects were exposed for 30 minutes in three different sessions to the stray field of the static magnetic field (SMF) of a 3 and a 1.5 T cylindrical Philips *Intera* magnet, and finally to a magnet in which the magnetic field was absent. No RF energy or switched gradient magnetic fields were utilized in this study (i.e., no MR images were acquired). The sequence of the exposure periods was unknown to the subjects, but was known to the researcher who administered the neurobehavioral tests (i.e., a single blind experimental set-up)[162]. After the session each subject was interviewed and asked about the applied value of the magnetic field during this session. The answers to these questions were random (i.e., correct answers did not differ significantly from 33%), indicating that the experiment was indeed a true single blind study. The sequence of exposure was the same for all subjects and was selected for practical reasons in terms of the organization of the experiments.

In addition to questions about basic information such as age, years of employment at the company, use of glasses, use of medication, colour-blindness, and familiarity with MRI scanners, a small questionnaire was administered before each session to all subjects regarding possible confounders such as the use of coffee, tea, and alcohol; tiredness; and stress. The subjects did not perform the tests at a fixed moment during a working day (e.g., early in the morning or late in the afternoon); rather, the tests were assigned at random for each measurement.

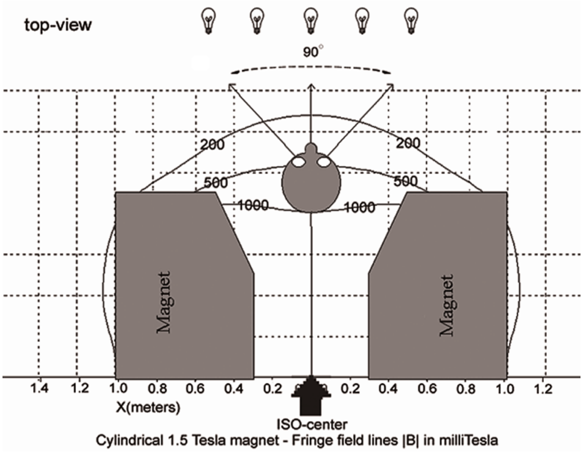


Figure 5.1. Position of the volunteer's head (top-view) in the stray field of the 1.5 Tesla cylindrical MRI-magnet. Additional head movements prompted by following a series of successively burning lights are indicated.

Each measurement session was divided into short periods of 20 seconds (exposure period), followed by periods of neurobehavioral testing (test period). In the exposure periods, the subject was placed (sitting on a chair as close as possible to the system) with his back to the bore of the MRI magnet facing outward. The centre of the subject's head was positioned approximately on the axis of symmetry of the actively shielded MRI magnet. The practical exposure level to the static magnetic field (SMF) for the head of the subject was approximately 600 mT for the 1.5 T scanner and 1 T for the 3.0 T scanner. To generate an additional dynamic magnetic field component, the subject had to follow a series of consecutively burning lights (one sequence took two seconds), provoking 10 side-side movements of the head of approximately 0.4 m/second. The angle of displacement (i.e., the change of direction in which the subject looks) was about 90°. The movement of the subject's head introduced a change of the magnetic field superimposed on the SMF, which led to a change in the field magnitude as well as the field direction over the volume of the subject's head (hereafter referred to as the "dynamic field"). Figures 5.1 and 5.2 show the position of the volunteer in front of the magnet, with top and side views of the actual situation, magnet field lines for the 1.5T and 3.0T magnets, and an indication of the motion of the head requested from the volunteers. The dynamic field components are considered to be the trigger for reported complaints such

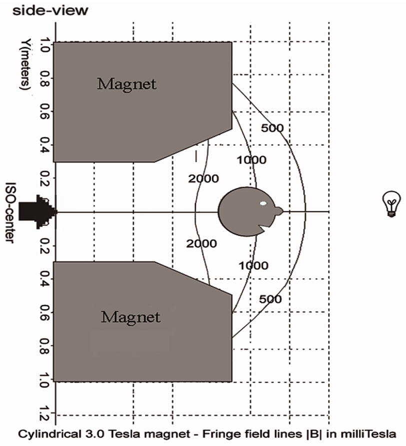


Figure 5.2. Position of the head of the volunteer's head (side-view) in the stray field of the 3.0 Tesla cylindrical MRI-magnet.

as dizziness, forgetfulness, etc.[25]. Time-varying magnet gradient fields generated by the gradient coils of the system were not applied during the study.

After the examination none of the subjects complained about dizziness or any of the other effects mentioned before.

Table 5.1. Description of the Neurological test battery.

Neurological Domain	Cognitive test	description
working memory	Visual memory	Reproduction of series of visual stimuli in reversed order
	Auditive memory	Reproduction of series of auditive stimuli in reversed order
Eye-hand coordination	Pursuit aiming II (2 repeats)	Placing dots in circles without touching the edge (speed)
		Correct places dots divided by total number of dots (precision)
	Pursuit aiming (small)	As Pursuit Aiming (speed), but with smaller circles
		As Pursuit Aiming (precision), but with smaller circles
visual	Visual tracking (2 versions)	Tracking of multiple tangled lines on paper
	Visual scanning	Scanning lists of numbers and marking all numbers '6'
	Vistech 6000 Contrastsensitivity*	Correct identification of lowest contrast of contrast patches composed of sinusoidal gratings at different spatial frequencies.

*** 5 different spatial frequencies (1.5, 3.0, 6.0, 12.0, 18.0 cycles per degree).**

Neurobehavioral effects

Immediately after each exposure period the subjects had to complete one test in the neurobehavioral test battery while still exposed to the SMF. Based on reported complaints[10] and results from our earlier study (chapter 3), the neurological testing battery consisted of a selection of tests aimed at measuring the effect of exposure to SMFs on working memory, visual inference, and eye-hand coordination neurological domains (Table 5.1). The eye-hand coordination (pursuit aiming II-test) and visual contrast sensitivity (Vistech VCTS 6000-test (Vistech consultants)) tests were similar to those used in our previous study (chapter 3). In addition, cognitive tests for visual or auditive processing of information (letter-number sequencing, Wechsler Adults Intelligence Scale (WAIS III) [111]), as well as tests to assess scanning and tracking of visual stimuli were added[111] in an attempt to localize the point of disturbance of the cognitive process. To assess a possible effect of exposure duration, the pursuit aiming II-test was administered twice: once after one minute of exposure to the magnetic field, and once after 25 minutes of exposure. To assess the effect of different levels of test difficulty, a version of the pursuit aiming II-test with smaller circles, as well as a more difficult and an easier version of the visual tracking tests, were administered.

As noted before in our previous study (chapter 3) and in other studies[113,116], most cognitive tests are subject to a learning or practice effect. To minimize or eliminate these effects a pre-study training session was held in which the complete test battery was explained and practiced once before the actual measurements were obtained. In addition, a relative long period of three weeks was used between the three consecutive sessions to further eliminate any residual learning effect. An overview of the test protocol is shown graphically in Fig. 5.3.

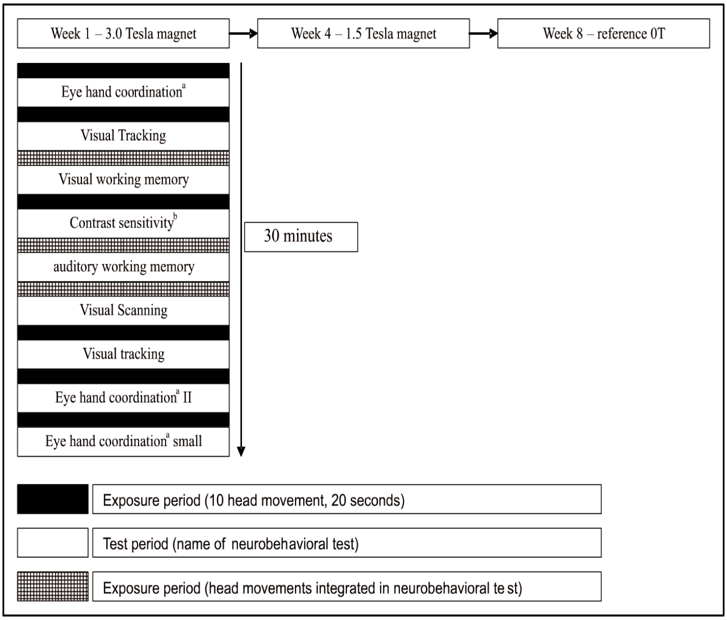


Figure 5.3. overview of the test protocol.

Statistical analyses

The study was performed with a case-crossover design[140], and can be regarded as a variant to a matched case-control study with the case and control units defined as different periods within a subject[142]. This design was kept for the statistical analyses. Generalized linear mixed models (GLMMs)[131] were applied using PROC MIXED in SAS version 8.02 (SAS systems, Cary, NC, USA):

$$Y_{ij}=(\mu + \alpha_i) + \beta_T{*}\text{Tesla} + (\beta_c{*}\text{confounder}) + \varepsilon_{ij} \qquad [1]$$

where:

Y_{ij} = test score for each of the neurobehavioral tests of the battery (normally distributed);
μ = intercept, or average test score of all individuals;
α_i = random intercept adjustment, or between-subject variance, with ($\alpha_i \sim N(0,\sigma^2_{\text{between subject}})$, where between-subject variance is approximately normally distributed with mean 0 and variance σ^2_{bs};
β_T*Tesla = average effect (fixed) of the magnetic field on the test score;
β_c*confounder = adjustment (fixed) for potential confounders;
ε_{ij} = residual error, or within-subject variance: ($\varepsilon_{ij} \sim N(0,\sigma^2_{\text{within subject}})$, where within-subject variance is approximately normally distributed with mean 0 and variance σ^2_{ws}.

Similarly to a common least-squares regression model, the intercept (μ) and the fixed parameter (β_T) of this model estimate the average test score of all individuals and the average effect of exposure to the magnetic field on all individuals. In addition, the random intercept adjustment (α_i) accounts for natural differences between individuals in terms of their baseline test performance. Random effects were modelled with a compound symmetric covariance matrix for within-subject covariance, which assumes similar correlations between repeated measurements, and a variance components covariance matrix for between-subject covariance, which assumes there is no correlation between subjects. Potential confounders such as consumption of coffee, tea, and alcohol; tiredness; and stress level, were added to the GLMM one by one to analyze their influence on test performance at different exposure levels. However, none were found to have a statistically significant (*P* < 0.10) effect on test performance, and consequently none were used in the final model. The test-scores were all Gaussian distributed, except for the VISTECH VCTS 6000^{TM} contrast sensitivity scores, which were analyzed after $\log_{10}$ conversions[163], and the visual scanning scores, which were $\log_e$-transformed. The residuals of the statistical models were all approximately Gaussian distributed.

Because of the relatively small amount of subjects examined, a statistical significance level of 10% was used, since *P*-values are a function of the magnitude of the differences at different exposures, the number of participants, and the standard deviation (SD) of test performance for this group of participants. Because we tested only 20 participants in this exploratory study, the magnitude of the difference in performance is a better indicator of any neurobehavioral effect than *P*-values alone.

RESULTS

Results were obtained for all 20 subjects, for a total of 60 measurements in a 10-week period. The mean test scores and SDs for all tests and magnetic field strengths are presented in Table 5.2.

Applying Eq. [1], statistically significant negative exposure-response relations of 2.1% and 1.0% per 100 mT were found for visual and auditive working memory, respectively (Table 5.3).

Significant exposure-response relations were seen for speed of eye-hand coordination of –0.9%, -1.1% and –0.7% per 100 mT for the first test (speed 1), the second test (speed 2), and the difficult version of the pursuit aiming II-test (speed small), respectively. No significant exposure-response relations were found for precision of eye-hand coordination (P = 0.88, P = 0.16, and P = 0.11, respectively).

In the visual domain, negative exposure-response relations of 3.1% and 3.0% per 100 mT exposure were found for both the more difficult and easier versions of the visual tracking tasks (*P* < 0.01). However, visual scanning speed and visual contrast sensitivity did not show any decline of performance with increasing exposure to SMFs.

Table 5.2. Average test performance and standard deviation for each neurobehavioral test near the 0, 1.5 and 3.0 Tesla system.

Neurological Domain	test battery	0 Tesla		1.5 Tesla**		3 Tesla ***	
		am[a]	std[b]	am[a]	std[b]	am[a]	std[b]
Working memory	visual	16.7	2.9	14.2	3.5	13.3	2.9
	auditive	12.6	2.6	11.9	2.7	11.3	2.3
Eye-hand coordination	speed 1	251.6	54.5	240.7	54.4	227.5	52.3
	speed 2 (25 min.)	268.0	59.4	266.2	55.0	237.1	51.1
	speed (small)	118.2	26.8	120.4	23.0	109.4	24.6
	precision 1	0.99	0.02	0.99	0.01	0.99	0.03
	precision 2 (25 min.)	0.99	0.01	0.98	0.03	0.98	0.04
	precision (small)	0.94	0.05	0.96	0.06	0.96	0.06
Visual	Visual tracking 1	42.9[c]	12.1	44.2[c]	10.8	56.5[c]	20.9
	Visual tracking 2	32.8[c]	11.0	36.5[c]	11.1	42.7[c]	17.2
	visual scanning	129.7[c]	50.1	143.8[c]	97.5	143.0[c]	95.7
	contrastsensitivity[d]						
	1.5	159.8	51.5	153.7	41.1	149.5	58.0
	3.0	279.9	83.6	295.1	103.2	257.2	70.0
	6.0	311.3	103.8	312.9	120.2	307.8	109.6
	12.0	189.4	89.6	186.4	93.3	180.7	92.3
	18.0	58.5	27.0	57.3	26.9	60.2	33.0

[a] arithmetic mean; [b] arithmetic standard deviation; [c] higher values means worse performance; [d] cycles per degree;
**** actual exposure level for the subject was about 0.6T;**
***** actual exposure level for the subject was about 1.0T.**

DISCUSSION

In this study we aimed to analyzing exposure-response relations between SMF strength and subject's performance on neurobehavioral tests. The working memory, eye-hand coordination, and visual neurological domains were evaluated. Negative exposure-response relations were found for visual and auditory working memory, eye-hand coordination speed, and visual tracking tasks during exposure to stray fields up to 1 T of magnets up to 3 T. Performance in eye-hand precision, scanning speed, and visual contrast sensitivity tests apparently did not depend on strength of the SMF.

In agreement with our previous study, in which performance at the pursuit aiming II-test was reduced by 4% during exposure to the stray magnetic fields of a 1.5 T magnet (approximately 700 mT), in this study performance in eye-hand coordination tests was reduced by

0.9%/100 mT for the first trial, and 1.1%/100mT for the second trail after 25 minutes of exposure. The smaller, more difficult version of the test was also reduced by 0.7% per 100 mT exposure. Whereas in the previous study eye-hand precision was affected, in the present study eye-hand coordination speed was affected. It remains unclear whether this difference is caused by differences in exposure to the SMF or the generated additional dynamic magnetic fields, or that it is an artefact of the study design. The absolute test scores in both studies are comparable for eye-hand coordination speed, but the eye-hand coordination scores show that fewer errors were made in the second study than in the first. I should be noted that the outcome precision and speed of the pursuit aiming II-test are closely related. Compensational behaviour might increase precision of eye-hand coordination, but might have a negative effect on speed.

Table 5.3. Estimated trends of performance at neurobehavioral tests and exposure to static magnetic fields.

Neurological Domain	test battery	*P*–value	Estimated trend per 100mT[a]
working memory	visual	<0.01	-2.1%*
	auditive	0.01	-1.0%*
Eye-hand coordination	speed 1	<0.01	-0.9%*
	speed 2	<0.01	-1.1%*
	speed small	<0.05	-0.7%*
	precision 1	0.88	-0.0%*
	precision 2	0.16	-0.1%
	precision (small)	0.11	+0.2%
visual	Visual tracking 1	<0.01	-3.1%*
	Visual tracking 2	<0.01	-3.0%*
	visual scanning	0.14	+0.5%
	Contrast sensitivity**		
	1.5	0.22	-0.8%
	3.0	0.16	-0.7%
	6.0	0.84	-0.1%
	12.0	0.62	-0.6%
	18.0	1.00	-0.0%

*** percentage calculated from mean test-score at 0 Tesla;**
**** contrast in cycles per degree**
[a] average trends based on mixed effects model in percentage per 100 milliTesla exposure.

Visual contrast sensitivity was also measured in both our previous study (chapter 3) and the current study. Although a statistically significant ($P < 0.10$) reduction was found during exposure to the stray magnetic fields of a 1.5 Tesla MRI magnet in our previous study, a statistical significant exposure-response relation was not found for any spatial frequency in the present study. Presumably this reflects the relatively small population examined and the large confidence intervals in the present study, since the strongest exposure-response relations of 0.8% per 100 mT ($P = 0.22$ and $P = 0.16$, respectively) were found at 1.5 and 3.0 cycles per degree, which are the same spatial frequencies that showed an effect previously. The results of the VISTECH VCTS 6000-test were analyzed after a $\log_{10}$ conversion, as suggested by Gilmore[163]. This was done because sensory systems respond in a logarithmic manner to changes in sensory stimulation. In our previous study the results were not $\log_{10}$-transformed; however, re-analyses did not significantly alter our previous findings.

For other tests in the visual domain that were not administered in our previous study, an exposure-response was found for visual tracking tasks of –3.1%/100 mT exposure for the difficult version and –3.0%/100mT for the easier version, but not for visual scanning speed tasks. The absolute scanning speed scores (Table 5.2) suggest that performance was reduced when the subjects were exposed to a magnetic field, but reduction in performance did not increase with increasing field strength. The large variance between subjects precluded finding any statistically significant findings.

Exposure-response relations were also found for the processing of information from visual (-2.1%/100 mT) and auditive (-1.0%/100 mT) stimuli. This suggests that the distortion of eye-hand coordination and visual-tracking tasks resulting from exposure to high magnetic fields occurs in the processing of the presented stimuli, and not so much in hearing or vision itself.

One of the major drawbacks of our previous study was the presence of a confounding improvement of test-performance by repetition of neurobehavioral tests (i.e., the learning or practice effect), which made correction for this learning effect essential. In this study we attempted to eliminate this effect by again performing a pre-study training, but also by using a three-week period between each repeated test instead of the one-week period used before. Although because of logistical problems we were not able to use a completely random distribution of subjects over exposures, these results do not support the presence of a strong learning effect that could have confounded the test outcomes. Nevertheless, any residual learning effect would be more profound in neurobehavioral tests that are repeated each session (e.g., pursuit aiming II, visual scanning), and less profound when different versions are presented during each session (e.g., visual and auditive working memory and visual tracking) or for the VISTECH VCTS 6000 test, which tests the sensitivity of the eyes to see contrasts. Furthermore, previous studies[118-120,164] have shown that the greatest practice effects occur between the first and the second trials (or in our study, between the pre-study training session and the first measurement). It should be noted, however, that randomly assigning the level of exposure to the three sessions in this study resulted in a sequence of exposure scenarios that would enhance any residual practice effect.

Together with the results from our previous study (chapter 3), this study confirms that eye-hand coordination and the visual domain are affected by exposure to SMFs. In addition, our results suggest that processing of visual and auditive information is also affected, and that an exposure-response relation exists for visual and auditive working memory, eye-hand coordination speed, and visual tracking tasks. However, since the stray fields to which the volunteers were exposed were very inhomogeneous, it was difficult to assess the actual exposure in a given time interval. Therefore, it remains unclear whether the speed of motion in combination with the gradient or the SMF strength is the more important factor in causing the neurobehavioral effects.

Other research in this area with even stronger magnets (8 T) did not show any effects on working memory tests[68]. However, the working memory task presented in our study, was of a more complicated nature, since letters and digits had to be remembered, separated, and reproduced while the subject followed a series of consecutively burning lights. In contrast, in the study by Chakeres et al.[68], a series of digits and letters had to be separated and reproduced immediately after they were presented. Furthermore, the volunteers in that study were placed inside the bore of the magnet (and were thus exposed to a much higher SMF) and did not perform additional standardized movements with their head and torso to generate an additional dynamic magnetic field.

Earlier studies on humans did not find the same effects observed in the present study[65,66,124,165]. This can be plausibly ascribed to the fact that our studies measured neurobehavioral performance during actual exposure to the static, gradient, and dynamic magnetic field instead of minutes to hours after exposure. This suggests that these effects are temporary and disappear shortly after exposure has stopped (chapter 2).

In conclusion, these results suggest that processing of visual and auditory information in the brain, and speed of eye-hand coordination are affected by exposure to static and local dynamic magnetic fields. In addition, it was shown that these effects depend on the strength of the SMF in which participants moved their heads, supporting the concept of a field-dependent biological mechanism (as previously suggested for sensory effects[54]). However, it remains unclear whether the actual performance of operating personnel during interventional therapy will be affected, since our findings resulted from a (worst-case) test situation involving frequent head movements. Nevertheless, with the increasing development and use of both interventional operation procedures and MRI systems with stronger magnets[25], these effects might become apparent. Additional research should examine these effects in different control groups and assess the potential side effects of interventional procedures and the use of even stronger magnets in these important medical diagnostic systems.

Chapter 6

Cognitive Effects of Exposure to Stray Fields Generated by a 7 Tesla Ultra-High Field MRI Magnet.

Frank de Vocht
Tobias Stevens
Paul Glover
Alan Sunderland
Penny Gowland
Hans Kromhout

NeuroImage; provisionally accepted.

ABSTRACT

Neurobehavioral performance during exposure to the magnetic stray field of a 7 Tesla MRI scanner was assessed, as well as the impact of exposure on cognition, which would confound fMRI studies.

27 volunteers completed four sessions, which exposed them to approximately 1600 milliTesla (twice), 800mT and negligible static field exposure. The order of exposure was assigned at random and was masked by placing volunteers in a tent to hide their position relative to the magnet bore. Volunteers completed a test battery assessing auditory working memory, eye-hand coordination and visual perception. During three sessions the volunteers were instructed to complete a series of standardized head movements to generate additional time-varying fields (~300 $mT \cdot s^{-1}$ and ~150 $mT \cdot s^{-1}$ r.m.s.). In one session, volunteers were instructed to keep their heads as still as possible.

Performance on a visual tracking task was negatively influenced ($P < 0.01$) by 1.3% $100mT^{-1}$. Furthermore, there was a trend for performance on two cognitive-motor tests to be decreased ($P < 0.10$). No effects were observed on working memory.

Taken together with results of earlier studies, these results suggest that there are effects on visual perception and hand-eye co-ordination, but these are weak and variable between studies. The magnitude of these effects may depend on the magnitude of time-varying fields and not so much on the static field. While it appears that the use of ultra-high field will not be a significant confound in fMRI studies of cognitive function, future work should assess whether they may impair performance of employees working in the vicinity of these magnets.

INTRODUCTION

Magnetic Resonance Imaging (MRI) is a powerful diagnostic imaging technique that has been in use since the late 1970s[10]. It has some clear advantages over the competing medical imaging techniques, but there are acute risks associated with the use of strong static magnetic fields, switched gradient fields and radio-frequency (RF) energy used in MRI. Patient and staff safety is maintained by eliminating magnetic objects from the vicinity of the magnet, screening patients for pace-makers and aneurysm clips before they undergo a scan, limiting the strength of the rapidly switching gradient fields to avoid peripheral nerve stimulation, minimizing radiofrequency induced heating and taking steps to avoid RF burns[10]. Besides these potential acute risks, no adverse health effects have been associated with MRI[10,66,67,71]. However, with the introduction of interventional MR procedures[40,148,149,160] that involve medical staff working in the vicinity of the scanner for extended periods, any potential effects of short and/or long-term exposure would be inevitably increased (chapter 4).

Presence in these stray fields has been related to an increase of subjective complaints such as dizziness, nausea, tiredness, headaches etc. (chapter 2, [54,166]). Furthermore, volunteer studies in the stray field of a 1.5 Tesla (T) (chapter 3) or of a 1.5 T and 3.0 T MRI magnet (chapter 5) have suggested that eye-hand coordination, visual contrast sensitivity, visual tracking tasks and working memory are negatively affected during exposure. Results from animal studies have also suggested that exposure to strong magnetic fields (7, 9.4 and 14.1 T) leads to a disturbance of the vestibular system[90] and to an increase of c-Fos expression, a marker for neural activation, similar to expression found after rotation[88].

In addition to concerns about possible hazards of exposure, it has become increasingly important for scientific reasons to establish whether strong magnetic fields might have any effect on neural processing. It is widely assumed that functional magnetic resonance imaging techniques offer non-invasive method of detecting and mapping human brain activation[167]. However, the increasing use of high and ultra-high fields makes it important to assess the validity of this assumption.

This manuscript describes a single-blind volunteer study of transient neurobehavioral effects of exposure to the stray field of a 7 T, whole-body, clinical MRI scanner, assessing the effects of exposure to the static stray field and of time-varying (dynamic) magnetic field components evoked by voluntary movement, extending the work previously carried out at lower field strengths (chapter 3 and 5).

METHODS

Population

This study was performed at the University of Nottingham, with local ethics committee approval. Twenty-seven volunteers were recruited for the experiments from a database of volunteers available at the department (n=6), from department members (n=3), or from students recruited through advertisements at university campus (n=18) (Table 6.1). Fourteen were female and 13 were male. Their age ranged from 18 up to 51 years, with a median age of 20 years. Education ranged from 1st-year undergraduate students to PhD. All study subjects underwent standard, local MR safety screening and were also asked to remove any metal objects, including metal in clothing, before the start of the measurements to ensure that they were blind to their exposure.

Table 6.1. Characteristics of study population and effect modifiers.

Population characteristics	levels	N
		27
Gender	Male	13
	Female	14
Age	Arithmetic mean (range)	25.0 (18-51)
Education	BSc	20
	MSc	3
	PhD	4
Hand of preference	Left	4
	Right	23
Glasses	Yes	13
	No	14
Reading difficulties	Yes	2
	No	24
	Unknown	1
Consumption of coffee within 2 hours prior to measurements	Yes (# cups)	7 (1-2)
	No	20
Consumption of alcohol evening prior to measurements	Yes (# glasses)	5 (2-7)
	No	22

Test sessions

Each volunteer performed the neurobehavioral test battery four times (twice at high , once at medium and once at low field strength). The battery took approximately 30 minutes to complete each time, with a short break in between sessions. The sequence of the exposure levels was assigned at random and the volunteers were unaware of their exposure during the sessions, although the exposure could not be masked for the researcher administering the neurobehavioral test battery. Three sessions (once at each field strength) included short periods where volunteers performed standardized head movements to generate a time varying magnetic field component (dB_0/dt). For the additional session at high field, the subject remained stationary.

Before the first test session, volunteers were asked to complete a short questionnaire on potential effect modifiers and confounders, (Table 6.1). After completing the questionnaire, the volunteers were blindfolded and guided to the magnet hall by one of the researchers. In the magnet hall, the volunteers were guided into a small tent (101cm by 109cm and 205cm high) to blind them to their distance from the magnet, and thus their exposure. Volunteers were instructed to remove their blindfold when

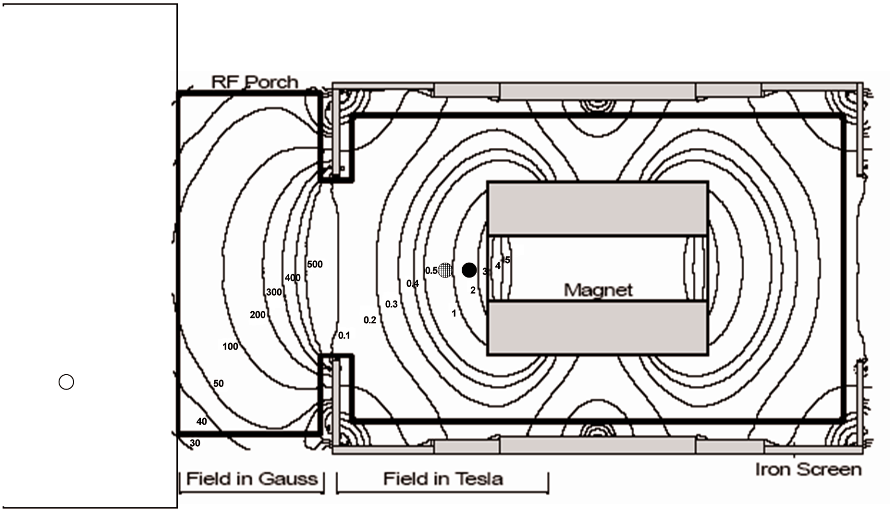


Figure 6.1. Overview of the magnetic stray field of the 7 Tesla magnet and approximate position of the volunteers* in all four sessions.
*: high exposure (~1600mT) in black, medium exposure (~800mT) in grey and un-exposed position outside the magnet room in white.

they were in the tent to enable them to sit down. A wooden chair, a small table, artificial lights and a bar with small red lights (described below) used to provoke standardized head movements during the exposure periods, were present.

Exposure to the static magnetic field

The tents in which the volunteers sat during the test sessions were placed at one of three pre-marked positions from the bore of the whole-body, 7 T 80 cm MAGNEX MRI magnet (Figure 6.1). No RF energy or switched gradients magnetic fields were used in this study. High exposure to the stray field was obtained by placing the chair with its back right against the bore of the magnet within the tent. Medium exposure was obtained by placing the tent at 52 cm from the bore of the magnet. This position was chosen to expose volunteers to a magnetic field strength comparable to that in a previous study performed around a 3.0 T clinical MRI magnet (chapter 5). Low exposure was obtained by placing the tent in a room adjacent to the room containing the 7 T magnet.

Additional movements

It has been postulated (chapter 3, 4, 5, and [66,71]) that sensory effects in static magnetic fields might be caused by movement in those fields and the resulting time-varying magnetic fields components (dB_0/dt). To investigate this, standardized head movements (described below) were performed at each exposure level, with one test session at high exposure carried out without head movements.

Four red lights were attached to a horizontal bar placed at eye level on the far side of the tent from where the volunteers sat. These lights could be illuminated in turn back and forth across the bar and volunteers were instructed to follow the lights, by moving only their head. This provoked a head movement over approximately 90° at a frequency of 5/8 Hz. After ten complete head movements, the lights were switched off and the first neurobehavioral test was administered to the volunteer.

The induced time-varying magnetic field was measured for one volunteer using an in-house built dB_0/dt meter, fixed laterally to the side of the head (sphenoid bone region) by means of a headband[166].

Neurobehavioral test battery

A neurobehavioral test battery was assembled from existing neurobehavioral tests[111] that evaluate auditory working memory, eye-hand coordination and the visual cognitive domain (Table 6.2). To further evaluate eye-hand coordination an existing neurobehavioral test, designed to detect visual spatial neglect[111] was adapted for use in this

Table 6.2. Description and Sequence of the Cognitive Tests in the Test Battery.

Cognitive domain	Neurobehavioral test	Description	Sequence within battery
Eye-hand coordination	Pursuit Aiming II	A subject has 60 seconds to place as many dots in small circles on a piece of paper with a pencil (2 trials). Outcome scores are the number of correctly placed dots (speed) and speed relative to total number of dots (precision)	1
Working memory	Digits & Letters (WAIS III)	A random series of digits and letters is presented with a pre-recorded tape. The subject needs to remember them during mandatory head movements. The letters need to be recalled in alphabetical order and the numbers in increasing order. A new (longer) series is presented the test stops when subject failed at three consecutive trials	2
Visual	VISTECH contrast sensitivity	Contrast between lines and background decreases. Subject needs to identify orientation of a grating at 5 different spatial frequencies. Outcome is a minimum contrast that can be identified.	3
Eye-hand coordination	Adapted line-bisection	Subject has to mark the middle point of 32 lines as fast as possible. Outcome scores are time (sec) and average deviation. series of 10 digits are presented verbally	4
Working memory	N-back	Subject says “yes” when the same digit is repeated immediately after a similar digits (1-back). After every three trials the number of digits between the 1st and 2nd similar Number increases with one the test stops when subject failed at three consecutive trials	5
Visual	Tracking	Subject needs to track entangled lines on paper with their eyes from left to right and mark where they end. Outcome scores are time to complete the test and errors	6

study by adding additional lines scattered on the test-form. Similar to the Pursuit Aiming II test, accuracy was assessed, but in contrast to the Pursuit Aiming II test, it had to be completed as quickly as possible instead of assessing performance in a given time period.

To minimize practice effects[113,117], different versions[115] of the WAIS III D&L, adapted line bisection, N-back and visual tracking tasks were used on each trial, with their order varying randomly across subjects. The sequence of the tests in the test battery is given in table 6.2.

Statistical analyses

Because volunteers switched from exposed to non-exposed (or visa versa) within the same study, the repeated measures study design could be regarded as case-crossover[140,168]. Linear mixed effects models were used to analyse the data[131], using SAS software version 8.02 (SAS systems, Cary, NC, USA). Performance on the neurobehavioral tests was adjusted for differences between the different test versions and for a practice effect. Furthermore, all statistical models were adjusted for significant ($P < 0.10$) potential confounding variables from the self-administered questionnaire.

The effect of the intensity of the magnetic field was assessed by analysing the measurements of the three test sessions at different fields including head movements (n=81). The effect of the time-varying field generated by the head movements was analysed by comparing the session without movements to the session with movements in the same static magnetic field (~1.6T) (n=54).

The following linear mixed effects model was used [Equation 1]:

$$Y_{ij} = \beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij} + \beta_3 x_{ij} + \beta_4 x_{ij} \ldots + \beta_p x_{ij} + U_{0j} + R_{ij}$$

where:

Y_{ij}= performance of a volunteer at a neurobehavioral test in each test session.

β_0= intercept, or underlying mean test performance

β_1= average change in test performance caused by exposure

β_2= adjustment for practice effect

β_3= adjustment for different test versions

β_4-β_p= adjustment for confounding variables

U_{0j}= random intercept adjustment to account for natural heterogeneity in test performance between volunteers (between-subject variance)

R_{ij}= residual, or within-subject variance

U_{0j} and R_{ij} resembled a Gaussian distribution (~N(0,$\sigma^2_{\text{between-subject or within-subject}}$), but the test performances at the adapted line-bisection test and the visual tracking tasks had to be $\log_e$ converted. The between-subject variance (U_{0j}) was modelled assuming no correlation between

Table 6.3. Weighted least squares means estimates of test performance, estimated trends per 100 milliTesla exposure and probability values of mixed effects models.

Neurobehavioral test battery			Exposure[a]				
domain	test	Test score	0 Tesla	~800mT	~1600mT	P-value	Trend[c]/100 mT (P-value)
Working memory	D&L WAIS III[1]	Correct repeats	9.76	9.40	9.93	0.3563	+0.01 extra (0.6078)
	N-back[2]	Max N-back	11.55	11.11	11.59	0.4234	+0.003 extra (0.8871)
Eye-hand coordination	Pursuit Aiming II[3]	Speed (# correct dots)	291.4	294.6	294.3	0.6702	+0.17 dots (0.4705)
		Precision	96.5%	95.8%	95.5%	0.2271	-0.06% (0.0930)
	Line-bisection[4]	Time (sec)	28.67	28.89	30.44	0.1400	+0.17 sec (0.0657)
		Deviation (mm)	2.49	2.40	2.31	0.2278	-0.45% (0.0839)
Visual	Tracking[5]	Time (sec)	39.27	45.18	49.20	0.0012	+1.32% (0.0003)
	VISTECH[6,b]						
	1.5	Score	60.84	66.33	60.37	0.6291	-0.03% (0.9672)
	3.0	Score	102.19	80.41*	97.95	0.1429	-0.21% (0.7817)
	6.0	Score	88.82	79.54	80.37	0.5560	-0.55% (0.6450)
	12.0	Score	34.71	30.76	31.30	0.6556	-0.60% (0.4745)
	18.0	Score	11.89	12.53	13.39	0.7383	+0.71% (0.4340)

Additional effect modifiers:
[1] education; [2] none; [3] none; [4] test version*practice effect (time only) and glasses yes/no; [5] practice effect/test version interaction; [6] none.
[a] weighted least squares means estimates from mixed effects models;
[b] cycles per degree;
[c] trend estimated by adding estimated exposure to B_0 to the statistical models as a continuous variable.

***: *P* = 0.0643**

the test scores of different volunteers (variance component structure). Within-subject variance (R_{ij}) was modelled assuming a similar correlation between different test scores for each volunteer (compound symmetric structure).

Test scores for the VISTECH contrast sensitivity tests where $\log_{10}$-transformed because the sensory systems respond in a logarithmic manner to changes in sensory stimulation[163]. Statistical significance was defined as *F*-test outcomes with a probability value less than 0.05 (<5%), and marginal differences were defined as F-test outcomes with a *P*-value less than 0.10 (<10%).

No correction for multiple comparisons were done[169], but instead the actual *P*-values[170] are provided in Tables 6.3 and 6.4.

RESULTS

Exposure assessment

For the high exposure level condition, the level of exposure at the head of a seated volunteer was approximately 1.5-2.0 T, depending on the height and posture of each volunteer. This reduced to approximately 0.8-1.0 T if a volunteer leaned forward during the head movements and 500-800mT when a volunteer was doing a neurobehavioral test requiring a pencil and paper. The medium exposure level was approximately 800 mT when the volunteer was seated in the chair. Exposure to the static magnetic field at the low exposure level was approximately 2 mT. The r.m.s. time-varying magnetic field, dB/dt, for one volunteer performing the standardized movements at the position closest to the magnet bore, was measured to be approximately 300 $\mathrm{mT{\cdot}s^{-1}}$. This was reduced by approximately a factor of two to 150 $\mathrm{mT{\cdot}s^{-1}}$ at the medium exposure position. No time-varying magnetic field was detected at the negligible exposure position.

Neurobehavioral test battery

Results of the neurobehavioral test battery for the three sessions with head movements are shown in Table 6.3. Analyses of confounding variables resulted in adjusting the “auditory working memory test” (D&L WAIS III) for level of education. The “adapted line-bisection test” was adjusted for different practice effect curves for different versions of the test as well as for wearing of glasses. The “visual tracking test” was adjusted for level of education education and also for different practice effect curves for different versions of the test.

As shown, only visual tracking performance differed significantly ($P < 0.01$) between different levels of static magnetic field exposure, and the magnitude of the effect also depended on the magnitude of the exposure ($p < 0.01$). Performance of the Pursuit Aiming II-test ($P = 0.09$) and the time to complete the line bisection-test ($P = 0.06$) showed a trend towards dependence on the magnitude of exposure, with borderline statistical significant differences. There was also a trend for the average deviance in the line bisection-test to improve with increased exposure ($P = 0.08$).

Table 6.4. Weighted least squares means estimates of test performance with and without mandatory head movements at ~1600mT of mixed effects models (n=54; $N_{volunteer}$=27).

Neurobehavioral test battery			Mandatory head movements		
domain	test	Test score	yes[a]	no[a]	P-value
Working memory	D&L WAIS III	Correct repeats	9.92	9.49	0.3297
	N-back	Max N-back	11.55	11.35	0.5629
Eye-hand coordination	Pursuit Aiming II	Speed (# correct dots)	293.64	293.62	0.9996
		Precision	95.5%	96.6%	0.0809
	Line-bisection[1]	Time (seconds)	30.67	29.34	0.1049
		Deviation (mm)	2.37	2.56	0.0585
visual	Tracking[1]	Time (seconds)	53.03	48.50	0.0683
	VISTECH[b]				
	1.5	Score	59.54	63.50	0.5510
	3.0	Score	96.65	105.46	0.4448
	6.0	Score	79.41	93.89	0.0757
	12.0	Score	30.95	32.85	0.5413
	18.0	Score	12.80	11.48	0.5206

[1] interaction not added to the model;
[a] weighted least squares means estimates from mixed effects models;
[b] cycles per degree.

Table 6.4 shows that head movements seemed to reduce precision on the Pursuit Aiming II-test ($P = 0.08$), time needed to complete the line bisection test ($P = 0.10$), visual tracking ($P = 0.06$) and the VISTECH test at 6.0 cycles per degree ($P = 0.08$), but none of these was significant at the 5%-level. In contrast, the average deviance at the line bisection-test appeared to be somewhat better with the mandatory head movements ($P = 0.06$).

DISCUSSION AND CONCLUSION

To our knowledge, this is the first study to assess transient neurobehavioral effects of exposure to the stray field of a 7 Tesla whole-body clinical MRI scanner. As far as we know, only two other studies assessed cognitive function at such high field strength, but in contrast to the present study cognitive performance was assessed in the homogeneous high magnetic field in the centre of the bore of an 8 T scanner, rather than in the stray fields gradients surrounding it, and without additional time varying fields. No effects[66], or only a small, but statistically significant, reduction on a short-term memory test (chapter 4)[68] were found in the earlier studies.

Two other studies have been conducted using a similar set-up to that described here, but at around lower field MRI systems and with slightly different neurobehavioral test batteries. These studies were the first to detect transient neurobehavioral effects of exposure to stray fields of MRI magnets. In the pilot study (chapter 3; study A), neurobehavioral effects of exposure in the stray field of a cylindrical 1.5 T MRI magnet were assessed, and in a follow-up study (chapter 5; study B) neurobehavioral effects of exposure to the stray fields of a 1.5 and of a 3.0 T MRI magnet was investigated. Study A included head and torso movements and study B included movements similar to those used here.

In the present study, the most prominent effect of exposure to the stray fields was on the time to complete the visual tracking task (1.3% 100mT^{-1}, $P < 0.01$), which supported the results found in study B (3.1% 100mT^{-1} and 3.0% 100mT^{-1}). Also in the visual domain, study A found an effect on visual contrast sensitivity, and the present study did show a trend for a reduced sensitivity at 3.0 c.p.d to exposure to 800mT ($P < 0.10$). However, no effect was seen at other spatial frequencies or field strengths. Whether this is a chance finding or whether the visual sensory system is especially sensitive to a specific intensity of the static magnetic field or dB/dt remains unclear. In future studies evaluating visual perception, more subjects should be tested, because large between-subject variance might have precluded finding significant results.

The results suggest that eye-hand coordination might also be negatively affected, as indicated by a trend for a decrease in accuracy on the Pursuit Aiming II-test of 0.06% $100mT^{-1}$, and time to complete the line bisection-test (0.6% 100 mT^{-1}). Impaired accuracy of Pursuit Aiming was also found in study A, while in study B speed but not accuracy was affected. The speed and accuracy of performance on a neurobehavioral test are likely to be closely related by compensation mechanisms (speed/accuracy trade-off), and this could explain the unexpected trend for improved accuracy of line bisection-test with increased exposure (-0.5% $100mT^{-1}$) in the present study.

Study B had found an effect on visual and auditory working memory, so we designed the present study to separate effects on working memory from any inference with the visual sensory system by using an additional auditory working memory test (N-back). However, in contrast to the results published for study B, no significant relation between exposure and auditory working memory was found in the present study.

Our results suggest that the observed effects may be associated to time-varying magnetic fields. There was a trend for performances in the eye-hand coordination domain (Pursuit Aiming II precision and line-bisection time) and in the visual sensory domain (visual tracking and VISTECH at 6 c.p.d.) to be worse when additional head movements were made prior to the test ($P < 0.10$). The importance of time-varying components of the magnetic field have previously been shown in a study where movement speed of MRI-technicians during work in magnetic fields and subjective health complaints were analysed (chapter 2).

A strength of the present study was that we were able to assign *a priori* the sequence of exposure randomly to each volunteer by varying distance from the magnet, using the movable tents to mask the actual exposure situation from the volunteers. Two different tents were used in this study. One tent was used for the sessions close to the magnet (~1600 mT and ~800 mT), whilst the second tent was used for the reference, negligible-exposure session. As noted, both tents were apparently identical and the chair, table and lights were moved between tents as required. Only a few volunteers actually noted that the tents might have been placed at different locations, and none noted that different tents were used. The sound of the cryostat-pump might have influenced performance as it was somewhat quieter for the low magnetic field exposure level.

Using multivariate statistical models we distinguished the effects of exposure from practice effects, but this design increased overall variability in test performance, and resulted in a decrease of statistical power. The larger size of the test group (27 versus 17 (previous study A) and 20 (previous study B)) only partially counterbalanced this effect. Exposure-response relations were evaluated by using the strength of the magnetic field as a continuous variable in the statistical models, assuming that any association between exposure to magnetic fields and neurobehavioral performance is linear. In practice an exposure-response curve might have any shape, and might even not be monotonic. However, more different magnetic field strengths need to be studied to investigate this.

It remains unclear what biological mechanism might underlie any observed effects. However, it is suggested[10,54] that sensory effects can be ascribed to the activation of highly sensitive sensory tissue by weak electrical currents, by weak magneto-hydrodynamic forces (in the semicircular canals), or by diamagnetic anisotropy (of the inner ear receptors). Since this and previous studies suggest that cognitive effects occur particularly in the visual sensory domain, a possible mechanism might be that the widely recognised ‘vertigo’ effect of moving in a magnetic field, might interfere with the vestibulo-ocular reflex[95]. The resulting instability of gaze might then lead to the observed impairments on perceptuo-motor tasks. This interpretation would indicate no direct interference with cognitive processing, which would be consistent with our observation of no impairment on the auditory working memory task.

In conclusion, these results suggest that exposure to the stray field of a cylindrical, whole-body 7 Tesla MRI scanner affects the visual sensory domain and to a lesser extent eye-hand coordination. The magnitude of the effects seems to depend on the magnitude of the dynamic field component generated by the additional movements and not on the strength of the static magnetic stray field itself. The effects found in this study should be related to actual performance during clinical use or interventional procedures, and exposure guidelines should take into account the effects of moving in magnetic fields as well as the strength of the static magnetic fields. In addition, this study suggests that field effects are not a significant confound in fMRI studies of normal cognitive function, but that it would be wise to consider the possibility of make allowance for some decrement in hand-eye coordination when assessing responses.

Chapter 7

GENERAL DISCUSSION

INTRODUCTION

The main objectives of this thesis were two-fold: (1) to assess type and frequency of health complaints as well as neurobehavioral effects that are experienced by engineers who assemble and test new magnetic resonance imaging systems, and (2) to investigate the relation between neurobehavioral performance and exposure to stray fields generated by high, very high, and ultra-high MRI magnets.

A number of self-reported acute symptoms experienced during working in the vicinity of MRI scanners could be related to exposure to magnetic stray fields and additional exposure to switched magnetic gradient fields and RF pulses during scanning. More specifically, the frequency of experienced vertigo, concentration problems, tiredness, metal taste and sensation of head ringing were related to the static magnetic field intensity, while especially tiredness was related to the duration of presence in the magnetic stray field.

Large differences in movement speed were found between different MRI engineers, which could therefore be regarded as a personal characteristic. In particular, moving rapidly in magnetic stray fields was related to the occurrence of headaches, vertigo, concentration problems, tiredness, metal taste and suggestions of head ringing.

The metal taste sometimes experienced during presence in stray fields of MRI magnets could not be contributed to mercury release from amalgam fillings, since no increased levels of mercury in urine were found after exposure. Urinary mercury levels were related to self-reported number of amalgam fillings, indicating that indeed a valid marker for amalgam fillings was measured. Other potential explanations of the findings are electrolysis of metallic fillings in the teeth induced from local current generation or excitation of sensitive nerve tissue in the tongue which results in a “random” experience of metallic taste.

Head movement of volunteers in stray fields generated by MRI scanners of 1.5 Tesla and higher, negatively affects the visual sensory as well as the cognitive-motor domain. The magnitude of these effects depends to a large extent on the magnitude of exposure to time-varying magnetic fields that are related to the magnitude of the spatial gradient field and movement speed in those fields. The data presented in this thesis also suggest that reported symptoms and cognitive effects disappear rapidly after exposure has ended, and no prolonged cognitive effects of exposure to magnetic stray fields could be shown.

Finally, the presented studies were inconclusive on whether working memory was affected by exposure to static or time-varying magnetic fields.

POOLED ANALYSES

Given a similar study set-up in the three experimental studies, the statistical issues of the relatively small sample sizes (and relaxation of the traditional 5% p-value to 10%) could to some extent be overcome by pooling the test outcomes for neurobehavioral tests included in all studies (i.e. the Pursuit Aiming-II cognitive-motor test and the VISTECH 6000™ visual contrast sensitivity test) and analyze them in a jointly fashion.

Table 7.1. Results pooled analyses of the Pursuit Aiming-II and VISTECH 6000™ test results.

Neurobehavioral test	Score	Trend/100mT[2] (CL[3])	P-value	Any exp.[4]	P-value
Eye-hand coordination	Speed	-0.01% (± 0.02)	0.88	-0.87%	0.34
	Precision	-0.09% (± 0.06)	<0.01	-1.37%	<0.01
Visual contrast sensitivity[1]	1.5 cpd	-1.35% (± 2.65)	0.38	-1.19%	0.20
	3.0 cpd	-1.03% (± 2.02)	0.41	-0.74%	0.07
	6.0 cpd	-1.02% (± 2.01)	0.20	-0.68%	0.16
	12.0 cpd	+2.69% (± 5.28)	0.75	+1.41%	0.83
	18.0 cpd	+6.47% (± 12.69)	0.39	+3.69%	0.87

[1] the stimulus expressed in cycles per degree (cpd); [2] trend estimated from data at 0 mT, 600mT, 700mT, 800mT, 1000mT and 1600mT; [3] 95% confidence limits; i.e. the estimated trend (β) is estimated with 95% certainty to be between β minus CL and β plus CL; [4] estimated average difference (and *P*-value) between test performance during any exposure to the static magnetic field (and resulting gradient and dynamic fields) and non-exposed sessions.

A pooled analysis using linear mixed effect models (Appendix) suggests (Table 7.1) that eye-hand coordination *precision* (-0.1%/100mT exposure), and not *speed* ($P = 0.88$), was statistically significantly reduced during exposure to magnetic fields up to 1 Tesla, and depended on the magnetic field strength.

The results of the combined analysis of the VISTECH 6000™-test do not show a statistical significant relation between magnetic field intensity and visual contrast sensitivity ($0.20 <= P <= 0.75$). However, the results do suggest that visual contrast sensitivity is hampered by exposure to magnetic fields as low as 600 mT, but that the magnitude of the effect is not related to magnetic field strength. In particular, a reduction in visual contrast sensitivity of 0.74% at 3.0 cpd compared with non-exposed measurements reached borderline significance ($P = 0.07$). The sensitivity curves presented in Figure 7.1 do suggest a (non-statistically significant) reduction in visual contrast threshold at contrasts between 2 cps and 6 cpd.

Whether the decrease in visual contrast threshold level did not dependent on the magnitude of exposure or whether the statistical power of these pooled analyses was not enough to reach statistical significance in the exposure-response analyses remains unclear. Alternatively, it has been postulated that a frequency-, as well as an intensity-"window" exists for exposure to electromagnetic fields within which biological effects are maximal[70,171-173]. Additional studies are needed to address these issues.

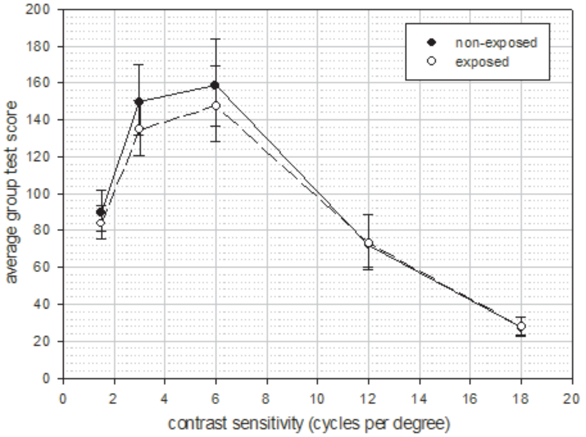


Figure 7.1. least squares estimates of VISTECH test-performance (and 95%-CL) when all studies are combined.

Several issues which may have influenced the study results need to be critically assessed, and in this chapter the choice of the study design, population, exposure assessment methods, health and neurobehavioral effect assessment methods and statistical methods will be critically reviewed.

Possible biological explanations of the shown effects as well as implications for occupational settings and directions for future research will be discussed as well.

CHOICE OF STUDY DESIGN AND POPULATION

Selection bias within the studies was not possible because cases acted as their own controls[141,174] in these experimental case-crossover studies. Furthermore, by using a repeated measurements design, these studies could be controlled for natural intra-individual biological and psychological differences[175-177] typically encountered in human experimental studies assessing magnetic field effects. The study with MRI engineers was not designed as a case-crossover, but exposed and control groups appeared to be comparable in distributions of age, socio-economic status, education, geographical area, and presumably only differed in their exposure to magnetic fields from MRI scanners.

Since specific groups of (company) volunteers were used in these studies, as is common practice in these types of studies[110], generalizability of these results to the general population could be an issue. Most of the studies in this thesis are performed with employees of one of the few companies that build MRI scanners. Individuals involved in applications in research or clinical settings however, were not part of the studies.

The observational study assessed effects of exposure to electric and magnetic fields (static, extremely low frequency (ELF) and radiofrequency (RF)) needed in the imaging process[28]. On the contrary, the experimental studies were done during exposure to the static magnetic stray field only, and exposure to switched gradient fields and RF-fields[26,28] were not taken into account. However, the relevant exposure metric to assess effects of exposure to static magnetic fields is still to a large extent unknown[2], especially since different physical mechanisms might be relevant for different levels, types, and sources of exposure[1]. Since these occur in different frequency ranges, it has been argued they should also be assessed separately[28].

STATISTICAL METHODS

Case-crossover designs analysed with linear mixed effects models[131,178-180] are generally more powerful than between-subject designs for expected subtle and transient effects[140,141,168] typically encountered in magnetic field research[181], and also take into account natural heterogeneity in test performance between different volunteers[175,176]. The random intercept mixed effects models[133,180] did not take into account inter-subject differences in practice effects and susceptibility to magnetic fields. Furthermore, modelling fixed effects slopes for the exposure-response relations did not take into account possible non-linear effects of magneto-biological processes[70,172,173]. The relatively limited number of subjects and repeated measurements per subject in these studies however, prohibited detailed analyses of these relations.

The covariance matrices in these studies were modelled using a *variance components* between-subject matrix and a *compound symmetric* within-subject matrix, assuming that natural heterogeneity between all subjects was similar, intra-individual correlation in test performances uncorrelated and inter-individual test performance similar for all subjects. Again, the relatively limited number of volunteers and repeated measurements did not allow for more detailed analyses of the structures of the between-subject and within-subject covariance matrices.

In these exploratory analyses with relatively small numbers of subjects and subtle effects, for which it has been argued that reducing type I errors should not be favoured over type II errors, the traditional *P*-value was relaxed to 10%[176,181-184]. It has been argued[185,186] that when a number of independent outcomes are tested against the null hypothesis this will dramatically increase the type I (Bonferroni inequality) and test statistics should be corrected before interpretation of the results[187,188]. However, similar findings in subsequent experimental studies is a better indicator of possible effects[189,190] than those based on rigorous use of *P*-values only[169,191]. Nevertheless, further confirmatory studies are required[184,190,191] to confirm the results and hypotheses generated in this thesis.

EXPOSURE ASSESSMENT METHODS

Static magnetic fields can be measured accurately using static magnetic field meters using a search coil or a Hall-probe[3], and even prototypes of personal dosimeters for monitoring exposure to static magnetic fields have been developed[192,193]. The intensity of the magnetic field at every position in the stray field can also be calculated accurately and graphical plots of the magnetic stray field can be created from measurements for every position around a magnet. Inherent to the properties of magnetic fields[27,194], static magnetic gradients will be different on different spatial positions around the magnet and can be very large on specific positions not only related to distance to the magnet, but also to the design of the magnet.

In our studies, exposure to magnetic fields was assessed by either:

(1) Defining *equal exposure zones* around the magnet along the magnetic field lines in the vicinity of the magnet.

(2) Measuring the static magnetic field in the area where volunteers were seated during neurobehavioral testing and assigning an average exposure to each position.

(3) Assigning scores for number and speed of movements in the stray fields to employees as a proxy for exposure to time-varying magnetic fields.

(4) Measuring time-dependent changes in magnetic field strength using an experimental measurement device (described in chapter 3, 5 and 6 (similar to [192])).

These methods only provided crude estimates of true individual exposure to magnetic stray fields. The first method assumes that exposure is equal throughout the whole *exposure zone*, while in fact there is a gradient present in the area outside the bore. By assigning the average exposure to a specific zone, it was assumed that the accumulated exposure over a longer time period (i.e. working day) was a good proxy for true exposure, or:

$$\sum_1^i \left(B_0(x) \text{-} t\right)_i \approx \int_0^{\infty} B_0(x)dt \qquad \text{(for zones } i\text{)}$$

This would have been true if B_0 on a specific spatial position was only related to the distance to the magnet. However, this also depends on magnet specific factors. Because no actual exposure measurements were done during this study, the magnitude and impact of this potential bias on assigned exposure levels remains unclear. Furthermore, even though it is known that the high spatial variability of the magnetic stray field will also have created a gradient in areas smaller than a volunteer's body, or head, our methods assumed that exposure was equal ($dB_0/dx=0$) in this area to provide a single exposure estimate. This implies that differences in effects caused by movement of the head (and resulting induced current and magneto-hydrodynamic effects) in this area, where $dB_0/dx>0$, have been ignored. The importance of this exposure relative to our exposure estimates is unknown.

Assigning similar exposure to all volunteers at a given position is an over-simplification of true exposure to the static magnetic field as well. Although positioned at the same positions, the high spatial variability in static magnetic gradient fields, as well as different physical characteristics of the volunteers, were likely to have caused individual variance from assigned exposure. However, combined with an end-point at the individual level, this a commonly used, and validated, method leading to negligible bias in exposure-response relations[178,195-198].

The proxy for dB_0/dt-exposure (assigned movement scores) for employees working in the RF-cage provided a semi-quantitative estimate of true exposure. This estimate could only be used for ranking of employees according to average number and speed of movements in a given time period, but does not provide any insight in actual levels of exposure, nor does it take into account peak-exposures. In the experimental studies prototypes of measurements devices were used for time-varying magnetic fields, but these were not extensively validated at the time of the studies and were consequently only used for relative ranking of volunteers and to provide group-estimates of average exposure.

As discussed previously, effects on cognition were only transiently present and disappeared rapidly after exposure had ended. However, maximal exposure to time-varying magnetic fields was achieved during additional head movements that were done in the magnetic stray field, but prior to test assessment. Although the impact on test performance is unclear, this implies that the effects on the cognitive-motor and visual sensory domains might have been an under-estimation of the true effects caused by additional movements of torso or head.

EFFECT ASSESSMENT METHODS

Test administration

Neurobehavioral effects were analyzed by selecting neurobehavioral tests assessing the cognitive-motor, cognitive and sensory domains[63,111], and were selected on three criteria:

(1) Assessing neurobehavioral domains relevant to exposure to magnetic fields (based on literature);

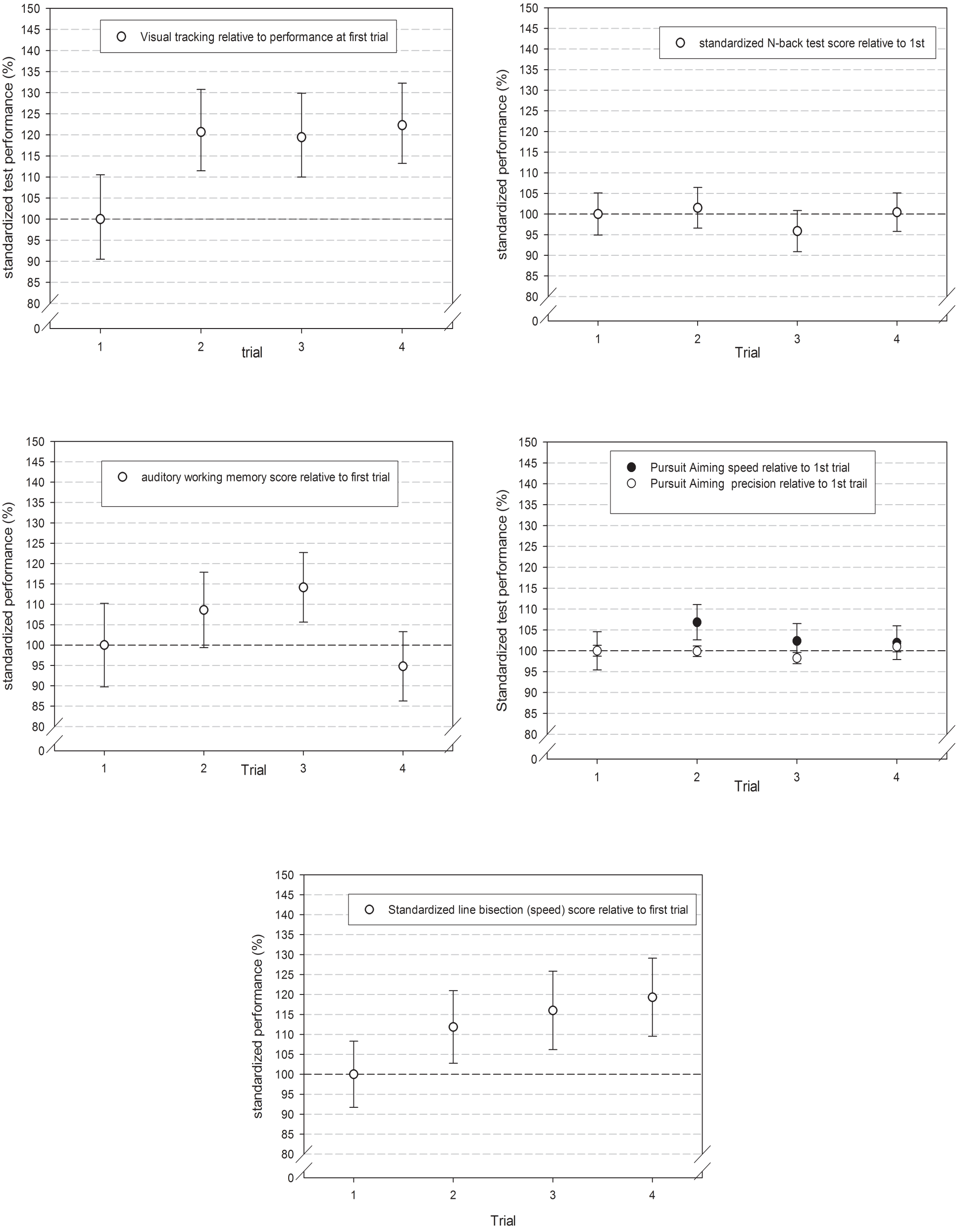
(2) Possibility of administering and completing the test during exposure to strong magnetic fields; i.e. tests should not contain any magnetic parts nor need electricity in the magnetic field;

(3) Evidence from previous studies showing cognitive domains affected by exposure to magnetic fields.

In addition, where possible, time dependent tests were selected, since these tests have a greater sensitivity to relative small or diffuse changes[63].

The use of these test batteries might theoretically have introduced two sources of measurement bias. First, the manual registration of the time-dependent tests could have introduced minor measurement error because of variable reaction times of researchers and subjects. Secondly, subjective input from researchers was required when a test required presentation of stimuli to the study subject, or the subject's response had to be registered by the researcher. Although most likely both sources of measurement error were non-differential, measurement error by the researchers could theoretically have been differential because of the single-blind study set-up. Since no significant differences in average test scores were found between both researchers and no significant in- or decrease in test assessment was found between the same tests done at the start and near the end of the study, measurement errors is assumed to have been minimal.

It remains unclear how the measured effects on the cognitive-motor and visual sensory domains should be extrapolated to functional performance of engineers, radiographers, nurses, and others when they



Figures 7.2.1-7.2.5. Estimated residual practice effect curves, relative to performance at the first trial for a number of neurobehavioral tests performed in the stray field of a 7.0 Tesla MRI magnet.

are working routinely in the vicinity of MRI scanners, since the relation between test performance and functional performance has not been explored frequently[63].

Residual practice effects

To minimize any practice effects that might bias neurobehavioral tests outcomes in non-randomized experimental studies, a recommended[116,117] pre-study training session, as well as alternate test versions[115], and prolonged periods[115] between subsequent trials were used.

The random design of the 7.0T-study allowed for estimation of the practice effects curves from the mixed effects models, which are presented graphically in Figures 7.2.1 to 7.2.5. The results suggest, in agreement with other studies assessing practice effects during repeated measurements[114-119,121], that practice effects were most prominent between the first and second trial and attenuated rapidly in consecutive trials. Practice effects (trials 2 and further) after the practice trial (#1) were only present for tests evaluating eye-hand coordination. These practice effects were thought to be much smaller than the -4.4% to -0.4% for the Pursuit Aiming II-test, and -3.7% to -2.8% for the adapted line-bisection test, respectively, since the actual trials were started after 1-3 weeks instead of a five minute break (in the 7T study).

These estimated practice effects were fairly similar to practice effects from a previous study[115], which were 17% and 9% between the first and second trail reported for different test batteries, with following sessions showing an attenuating effect from 8% to <1% and 2% to <1% in four consecutive sessions for different test batteries. This suggests that the relation between neurobehavioral effects and exposure to static magnetic stray fields from MRI scanners can only to a lesser extent be ascribed to residual practice effects.

Implications for aetiological mechanisms

Although the studies described in this thesis were not designed specifically to address questions on biological mechanisms of effects of exposure to strong static magnetic fields, the results provide additional evidence, in supplement to direct depolarization of nerve and sensory tissue, diamagnetic anisotropy and magneto-hydrodynamic mechanisms[13,54], for likely biological mechanism. Additional research however, is needed to establish any causal mechanisms for exposure leading to biological effects.

The extent and severity of a number of symptoms and performance at tests assessing the cognitive-motor and visual sensory domains, were related to intensity and duration of exposure, similar to proposed mechanisms for motion sickness[93]. This suggests that people susceptible to magnetic field exposure might be the same as those susceptible to motion sickness. However, so far no single physiological or psychological parameter has been found of high enough sensitivity and specificity to categorize individual motion sickness susceptibility[95].

As hypothesised, effects on the cognitive-motor and visual sensory domains could be contributed to gaze-instability by disturbance of the vestibu-ocular reflex[99]. In agreement with this, other studies have shown that subjects susceptible to motion sickness have a more intense vestibular reaction[95] and higher gaze instability[95,199], described by delayed or impaired visual scanning and perception[200] and onset of saccadic eye movement[201], and an elevation in contrast threshold[202].

Although still largely unknown[80,203], it has been proposed[203] that magnetic pulses can randomly activate, or cause a breakdown in[204], a subpopulation of neurons which suppresses coordinated processes in neural networks[205,206]. These can be very sensitive to small voltages applied diffusively across elements of the network, depending on the frequency[206] and intensity of the stimulus[73,200,203]. The resulting competition of the visual stimulus and the artificially induced excitation results in excitation as well as a suppression of visual perception[75,80,204,207,208], already below threshold for neuron excitation[209,210].

Similar to the neurobehavioral studies presented in this thesis, TMS studies expose subjects to time-varying magnetic fields. There are a number of differences between TMS studies and the experimental exposure-based studies presented in this thesis. The magnetic pulses in TMS studies are more focal than the exposed area during movement in stray fields of MRI scanners (i.e. the whole human body)[204]. Furthermore, the pulses in TMS studies have a higher intensity (up to 2 Tesla) and are shorter (typically 100-500 μs[73]) than those induced in this thesis, resulting in much higher exposure to time-varying magnetic fields (dB_0/dt). The results in this thesis do show however, that similar effects can already be measured at much lower exposure.

Working Memory

Whether working memory[211-213] is affected by exposure to magnetic fields remains an important issue with possible implications for occupational exposure limits, but also for functional MRI studies. Results from (r)TMS studies suggest that working memory can be affected by applying magnetic pulses to the brain cortex[204,214]. The results presented in this thesis however are contradictious, but nevertheless suggest that if working memory is affected by exposure to magnetic fields, effects are probably not significant enough to disturb findings of fMRI studies at the presently used magnetic field strengths.

In two other recent volunteer studies in the homogeneous static magnetic field in the magnet bore of an 8 T system[66,68], effects on working memory were not found, although a subtle effect on short-term memory was noted[68]. When effects on working memory were found however, these were found in studies where working memory was assessed during actual exposure (chapter 5) and not when assessed immediately after exposure had ended (chapter 2), or in a homogeneous magnetic field[66,68]. This suggests that if working memory is affected, these are only transient, and not clinically harmful effects presumably also caused by time-varying magnetic fields. Nevertheless, additional research is needed to resolve this issue.

IMPLICATIONS

The results from this thesis implicate that movement speed while working around MRI scanners should be minimized to reduce a number of symptoms from occurring, and possibly hampering the actual work being performed. Although relevant for all people working with or near these scanners, especially operating teams working on interventional MR systems should be made consciously aware of this. Relatively small effects that are not immediately noticed (like symptoms as dizziness and vertigo) on the cognitive-motor or the visual sensory domain might theoretically have serious consequences for this group, especially when interventional systems with higher magnetic field strength, or with actively shielded magnets with an increased spatial gradient field, will be developed. However, whether the effects described in this thesis will lead to an increase in errors when interventional procedures will be done using stronger magnets in the (near) future can, and should, be monitored.

Development of personal dosimeters might be used in the future to register dB_0/dt-exposure and could provide an early warning when movement speed has exceeded a relevant, yet to set, limit value. However, at present these personal dosimeters are not yet commercially available.

For the development of new dedicated interventional MRI systems, the results from the studies presented in this thesis imply that magnets should be developed such that magnetic gradient "hot-spots" do not occur in areas where surgical teams in hospitals, and to a lesser extent MR engineers, need to be present on regular basis, or for long periods at a time.

Furthermore, although additional research is needed to address this issue, these results could imply that it is advisable to avoid the use of actively shielded magnets to minimize high field gradients for newly built dedicated interventional MR-sites at higher field strength then used at present.

FUTURE RESEARCH

The number of studies assessing occupational exposure, subjective health complaints, biological parameters and neurobehavioral performance are still only limited, and a number of existing gaps in knowledge about the relevant exposure metric, occupational exposure levels and biological mechanisms have been identified[1]. Although the data presented in this thesis suggests that the effects of exposure to static magnetic stray fields of MRI scanners addressed in this thesis are not clinically harmful and disappear rapidly after exposure has finished, they should be studied in more detail, similar to other non-clinical transient effects at the work floor that could hamper working performance, well-being and possibly health[215-218].

Furthermore, these issues should be assessed in the near future, since if these gaps continue to exist, most likely problems concerning setting of valid exposure limits for present and future applications in MRI[29,219] will become more evident.

Associations between exposure to static magnetic fields and health or sensory effects could, in the few cases that replication studies were undertaken, not be replicated[1,176,206]. Therefore, replication of the studies presented in this thesis, as well as studies from other research groups[66,68,166], is urgently needed[220]. The case-crossover design seems a valid and sensitive approach to study these subtle and transient effects and should be applied in future studies assessing effects of the static magnetic field (in the magnet bore), and spatial gradient and time-varying magnetic fields of stray fields. Future studies should focus on an *a priori* hypothesized cognitive or sensory domain and focus on a limited number of different tests because administering neurobehavioral test batteries is very time-consuming, especially in a case-crossover design were volunteers need to complete the same test battery multiple times. In the absence of measurement devices these can be conducted using semi-quantitative methods to assess exposure, such as "exposure zones" and ranking of subject according to movement speed or indicative dB_0/dt values, similar to the studies presented in this thesis.

Studies on larger study populations should assess non-linear exposure-response relations, since complex non-linear dependencies for biological effects[70,172,173] have been found in studies assessing magneto-biological mechanisms. This might have important consequences for the use of (interventional) MRI scanners at higher field strength, as well as for setting and formulation of occupational exposure limits.

The studies in this thesis also did not take into account frequency-, and intensity-"windows" for magneto-biological effects. Future studies should assess these as well to measure a valid exposure metric and derive appropriate exposure limits.

Differences in magnetic field susceptibility between different individuals should also be studied, and these are present, whether it can be predicted in advance. A relation between motion sickness and vestibulo-ocular reflexes (VOR)[95,199,221,222] or salivary amylase levels[222,223] has been studied, but no easy too apply screening method was found. A standard questionnaire has been developed[224] to quantify individual susceptibility to motion sickness. Future studies should assess the applicability of this questionnaire, or of specially modified versions, to assess its correlation with susceptibility for magnetic field exposure. Ultimately, this might lead to screening of new employees in the MR manufacturing or clinical settings for magnetic field susceptibility before they routinely work with these systems.

Of prime concern for future studies is the development and validation of measurement devices to measure personal exposure to such high static magnetic fields, spatial gradient fields and time-dependent magnetic fields from MRI scanners. Also, without proper personal measurement devices, establishing relevant occupational exposure guidelines and regulations and controlling those will continue to be problematic. Similar to personal measurement devices used to measure other exposures, these measurement devices should not constrain movement or hamper with the work being performed. But more importantly, since the most relevant exposure metric still has to be established, measurement devices should be developed to, ideally simultaneously, measure B_0, dB_0/dx and dB_0/dt, and provide estimates of the time-weighted averages (TWA) and peak exposures. Comparable prototypes of a measurement device for dynamic magnetic fields have been used in this thesis, of which one has also been validated and used in a study on sensory experiences of human volunteers[166]. Prototypes of devices to measure exposure to the static magnetic field have been developed[192,193].

Alternatively, especially in a situation with an immovable source such as an MRI scanner, detailed field plots for the static field[1,27] and the spatial gradient field can be calculated for all spatial positions around a magnet and, in combination with observations of the movement patterns of employees through the stray fields, fairly similar to the crude method using "equal exposure zones" described in this thesis, be related to a subject's personal exposure. These methods however will only be relevant for quasi-experimental studies, but cannot predict personal exposure in different occupational settings and make inferences about exposure guidelines and regulations.

Finally, it remains unclear how the effects on neurobehavioral performance are related to the occurrence of acute health complaints or to decreases in performance during work. Future studies are needed to assess the correlation between performance at these neurobehavioral tests and performance during working conditions in MR manufacturing, research and clinical MRI use.

1. WHO. Environmental Health Criteria 232. Static Fields. Geneva, World Health Organization (WHO), 2006.
2. Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. *Environ Health Perspect* 2001;**109 Suppl 6:**911-33.
3. ICNIRP. Guidelines on limits of exposure to static magnetic fields. *Health Phys* 1994;**66:**100-106.
4. Salvatore JR, Weitberg AB, Mehta S. Nonionizing electromagnetic fields and cancer: a review. *Oncology (Williston Park)* 1996;**10**(4)**:**563-70; discussion 573-4, 577-8.
5. Repacholi MH, Greenebaum B. Interaction of static and extremely low frequency electric and magnetic fields with living systems: health effects and research needs. *Bioelectromagnetics* 1999;**20**(3)**:**133-60.
6. Feychting M. Health effects of static magnetic fields—a review of the epidemiological evidence. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**241-6.
7. Azanza MJ, del Moral A. Cell membrane biochemistry and neurobiological approach to biomagnetism. *Prog Neurobiol* 1994;**44**(6)**:**517-601.
8. Deichmann W, Henschler D, Holmstedt B, Keil G. What is there that is not a poison? A study of the Third Defense by Paracelsus. *Arch Toxicol* 1986;**58:**207-213.
9. Gilbert W. The Magnete. Mineola, NY: Dover Publications, 1991.
10. Shellock FG. Magnetic Resonance Procedures: Health Effects and Safety. Boca Raton: CRC Press, 2001.
11. Mourino MR. From Thales to Lauterbur, or from the lodestone to MR imaging: magnetism and medicine. *Radiology* 1991;**180**(3)**:**593-612.
12. Macklis RM. Magnetic healing, quackery, and the debate about the health effects of electromagnetic fields. *Ann Intern Med* 1993;**118**(5)**:**376-83.
13. Schenck JF. Physical interactions of static magnetic fields with living tissues. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**185-204.
14. Harlow T, Greaves C, White A, Brown L, Hart A, Ernst E. Randomised controlled trial of magnetic bracelets for relieving pain in osteoarthritis of the hip and knee. *BMJ* 2004;**329**(7480)**:**1450-4.

15. Wolsko PM, Eisenberg DM, Simon LS, et al. Double-blind placebo-controlled trial of static magnets for the treatment of osteoarthritis of the knee: results of a pilot study. *Altern Ther Health Med* 2004;**10**(2)**:**36-43.
16. Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *J Altern Complement Med* 2005; **11**(3)**:**495-509.
17. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000;**406**(6792)**:**147-50.
18. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. *Arch Gen Psychiatry* 1999;**56**(4)**:**300-11.
19. George MS, Wassermann EM, Post RM. Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *J Neuropsychiatry Clin Neurosci* 1996;**8**(4)**:**373-82.
20. Loo C. Transcranial magnetic stimulation: promise for the future? *Australas Psychiatry* 2004;**12**(4)**:**409-10.
21. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol* 2003;**2**(3)**:**145-56.
22. Bloch F. Nuclear induction. *Phys. Rev.* 1946;**70**(7-8)**:**460-474.
23. Lauterbur P. Image formation by induced local interactions - examples employing nuclear magnetic-resonance. *Nature* 1973;**242**(5394)**:**190-191.
24. Mansfield P, Grannell PK. Nmr diffraction in solids. *J. Phys. C-Solid State Phys.* 1973;**6**(22)**:**L422-L426.
25. Hu X, Norris DG. Advances in high-field magnetic resonance imaging. *Annu Rev Biomed Eng* 2004;**6:**157-84.
26. Gowland PA. Present and future magnetic resonance sources of exposure to static fields. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**175-83.
27. Crozier S, Liu F. Numerical evaluation of the fields induced by body motion in or near high-field MRI scanners. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**267-78.
28. Bassen H, Schaefer DJ, Zaremba L, Bushberg J, Ziskin M, Foster KR. IEEE Committee on Man and Radiation (COMAR) Technical Information Statement "exposure of medical personnel to electromagnetic fields from open magnetic resonance imaging systems". *Health Phys* 2005;**89**(6)**:**684-9.

29. Hill DL, McLeish K, Keevil SF. Impact of electromagnetic field exposure limits in Europe: is the future of interventional MRI safe? *Acad Radiol* 2005;**12**(9)**:**1135-42.

30. Jonsson P, Barregard L. Estimated exposure to static magnetic fields for the staffs of NMR-units. *Occup Med (Lond)* 1996;**46**(1)**:**17-9.

31. European Commission Directorate V. Public Health and Safety at Work - Non ionizing radiation: Sources, Exposure and Health Effects. Luxembourg: European Commission, 1996.

32. Lee JH, Lee HC, Kim HD, et al. How much are anesthesiologists exposed to electromagnetic fields in operating rooms? *Yonsei Med J* 2003;**44**(1)**:**133-7.

33. Hakansson N, Floderus B, Gustavsson P, Johansen C, Olsen JH. Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. *Occup Environ Med* 2002;**59**(7)**:**481-6.

34. Hakansson N, Stenlund C, Gustavsson P, Johansen C, Floderus B. Arc and resistance welding and tumours of the endocrine glands: a Swedish case-control study with focus on extremely low frequency magnetic fields. *Occup Environ Med* 2005;**62**(5)**:**304-8.

35. Edelstein WA, Hutchison JM, Johnson G, Redpath T. Spin warp NMR imaging and applications to human whole-body imaging. *Phys Med Biol* 1980;**25**(4)**:**751-6.

36. Di Salle F, Esposito F, Elefante A, et al. High field functional MRI. *Eur J Radiol* 2003;**48**(2)**:**138-45.

37. Henk CB, Higgins CB, Saeed M. Endovascular interventional MRI. *J Magn Reson Imaging* 2005;**22**(4)**:**451-60.

38. Hall WA, Liu H, Martin AJ, Truwit CL. Minimally invasive procedures. Interventional MR image-guided neurobiopsy. *Neuroimaging Clin N Am* 2001;**11**(4)**:**705-13.

39. Martin AJ, Hall WA, Liu H, et al. Brain tumor resection: intraoperative monitoring with high-field-strength MR imaging-initial results. *Radiology* 2000;**215**(1)**:**221-8.

40. Razavi R, Hill DL, Keevil SF, et al. Cardiac catheterisation guided by MRI in children and adults with congenital heart disease. *Lancet* 2003;**362**(9399)**:**1877-82.

41. Daanen V, Coste E, Sergent G, Godart F, Vasseur C, Rousseau J. Accurate localization of needle entry point in interventional MRI.

J Magn Reson Imaging 2000;**12**(4)**:**645-9.

42. Omary RA, Unal O, Koscielski DS, et al. Real-time MR imaging-guided passive catheter tracking with use of gadolinium-filled catheters. *J Vasc Interv Radiol* 2000;**11**(8)**:**1079-85.
43. Rickers C, Seethamraju RT, Jerosch-Herold M, Wilke NM. Magnetic resonance imaging guided cardiovascular interventions in congenital heart diseases. *J Interv Cardiol* 2003;**16**(2)**:**143-7.
44. Lardo AC. Real-time magnetic resonance imaging: diagnostic and interventional applications. *Pediatr Cardiol* 2000;**21**(1)**:**80-98.
45. Guttman MA, Lederman RJ, Sorger JM, McVeigh ER. Real-time volume rendered MRI for interventional guidance. *J Cardiovasc Magn Reson* 2002;**4**(4)**:**431-42.
46. Liu H, Hall WA, Martin AJ, Maxwell RE, Truwit CL. MR-guided and MR-monitored neurosurgical procedures at 1.5 T. *J Comput Assist Tomogr* 2000;**24**(6)**:**909-18.
47. Budinger TF, Lauterbur PC. Nuclear magnetic resonance technology for medical studies. *Science* 1984;**226**(4672)**:**288-98.
48. Budinger TF. Nuclear magnetic resonance (NMR) in vivo studies: known thresholds for health effects. *J Comput Assist Tomogr* 1981;**5**(6)**:**800-11.
49. Saunders RD, Smith H. Safety aspects of NMR clinical imaging. *Br Med Bull* 1984;**40**(2)**:**148-54.
50. Klucznik RP, Carrier DA, Pyka R, Haid RW. Placement of a ferromagnetic intracerebral aneurysm clip in a magnetic field with a fatal outcome. *Radiology* 1993;**187**(3)**:**855-6.
51. Kanal E, Shellock FG. MR imaging of patients with intracranial aneurysm clips. *Radiology* 1993;**187**(3)**:**612-4.
52. Luechinger R. Cardiac Pacemakers and ICDs: Laboratory Experience. ISMRM Workshop on MRI Safety: Update, Practical Information, and Future Implications. McLean, Virginia, USA: ISMRM, 2005.
53. Gimbel JR, Bailey SM, Tchou PJ, Ruggieri PM, Wilkoff BL. Strategies for the safe magnetic resonance imaging of pacemaker-dependent patients. *Pacing Clin Electrophysiol* 2005;**28**(10)**:**1041-6.
54. Schenck JF. Safety of strong, static magnetic fields. *J Magn Reson Imaging* 2000;**12**(1)**:**2-19.
55. Murayama M. Orientation of sickled erythrocytes in a magnetic field. *Nature* 1965;**206**(982)**:**420-2.

56. Brody AS, Embury SH, Mentzer WC, Winkler ML, Gooding CA. Preservation of sickle cell blood-flow patterns during MR imaging: an in vivo study. *AJR Am J Roentgenol* 1988;**151**(1)**:**139-41.

57. Tokimura H, Di Lazzaro V, Tokimura Y, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *J Physiol* 2000;**523 Pt 2:**503-13.

58. Feychting M, Ahlbom A, Kheifets L. EMF and health. *Annu Rev Public Health* 2005;**26:**165-89.

59. Kundi M, Mild K, Hardell L, Mattsson MO. Mobile telephones and cancer—a review of epidemiological evidence. *J Toxicol Environ Health B Crit Rev* 2004;**7**(5)**:**351-84.

60. Crasson M. 50-60 Hz electric and magnetic field effects on cognitive function in humans: a review. *Radiat Prot Dosimetry* 2003;**106**(4)**:**333-40.

61. Brent RL. Reproductive and teratologic effects of low-frequency electromagnetic fields: a review of in vivo and in vitro studies using animal models. *Teratology* 1999;**59**(4)**:**261-86.

62. Leszczynski D. Rapporteur report: cellular, animal and epidemiological studies of the effects of static magnetic fields relevant to human health. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**247-53.

63. Assessment: neuropsychological testing of adults. Considerations for neurologists. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1996;**47**(2)**:**592-9.

64. Bartels M, Mann K, Matejcek M, al. e. MRI and safety: EEG and neuropsychological findings before and after MR. *Forschr Rontgenstr* 1986;**145:**383-385.

65. Besson JA, Foreman EI, Eastwood LM, Smith FW, Ashcroft GW. Cognitive evaluation following NMR imaging of the brain. *J Neurol Neurosurg Psychiatry* 1984;**47**(3)**:**314-6.

66. Kangarlu A, Burgess RE, Zhu H, et al. Cognitive, cardiac, and physiological safety studies in ultra high field magnetic resonance imaging. *Magn Reson Imaging* 1999;**17**(10)**:**1407-16.

67. Chakeres DW, Kangarlu A, Boudoulas H, Young DC. Effect of static magnetic field exposure of up to 8 Tesla on sequential human vital sign measurements. *J Magn Reson Imaging* 2003;**18**(3)**:**346-52.

68. Chakeres DW, Bornstein R, Kangarlu A. Randomized comparison of

cognitive function in humans at 0 and 8 Tesla. *J Magn Reson Imaging* 2003;**18**(3)**:**342-5.

69. WHO. Proceedings: WHO workshop on Electrical Hypersensitivity. 2004.
70. Zhadin MN. Review of russian literature on biological action of DC and low-frequency AC magnetic fields. *Bioelectromagnetics* 2001;**22**(1)**:**27-45.
71. Schenck JF, Dumoulin CL, Redington RW, Kressel HY, Elliott RT, McDougall IL. Human exposure to 4.0-Tesla magnetic fields in a whole-body scanner. *Med Phys* 1992;**19**(4)**:**1089-98.
72. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;**1**(8437)**:**1106-7.
73. Jahanshahi M, Rothwell J. Transcranial magnetic stimulation studies of cognition: an emerging field. *Exp Brain Res* 2000;**131**(1)**:**1-9.
74. Meyer BU, Diehl R, Steinmetz H, Britton TC, Benecke R. Magnetic stimuli applied over motor and visual cortex: influence of coil position and field polarity on motor responses, phosphenes, and eye movements. *Electroencephalogr Clin Neurophysiol Suppl* 1991;**43:**121-34.
75. Kammer T, Puls K, Erb M, Grodd W. Transcranial magnetic stimulation in the visual system. II. Characterization of induced phosphenes and scotomas. *Exp Brain Res* 2005;**160**(1)**:**129-40.
76. Van Bladel J. The nature of electromagnetic stimuli. *Prog Clin Biol Res* 1988;**257:**1-21.
77. Reilly JP. Peripheral nerve stimulation by induced electric currents: exposure to time-varying magnetic fields. *Med Biol Eng Comput* 1989;**27**(2)**:**101-10.
78. Schaefer DJ, Bourland JD, Nyenhuis JA. Review of patient safety in time-varying gradient fields. *J Magn Reson Imaging* 2000;**12**(1)**:**20-9.
79. Schaefer DJ. Safety aspects of switched gradient fields. *Magn Reson Imaging Clin N Am* 1998;**6**(4)**:**731-48.
80. Kammer T, Puls K, Strasburger H, Hill NJ, Wichmann FA. Transcranial magnetic stimulation in the visual system. I. The psychophysics of visual suppression. *Exp Brain Res* 2005;**160**(1)**:**118-28.
81. Rosen AD. Membrane response to static magnetic fields: effect of exposure duration. *Biochim Biophys Acta* 1993;**1148**(2)**:**317-20.

82. Rosen AD, Lubowsky J. Modification of spontaneous unit discharge in the lateral geniculate body by a magnetic field. *Exp Neurol* 1990;**108**(3)**:**261-5.

83. Winther FO, Rasmussen K, Tvete O, Halvorsen U, Haugsdal B. Static magnetic field and the inner ear. A functional study of hearing and vestibular function in man after exposure to a static magnetic field. *Scand Audiol* 1999;**28**(1)**:**57-9.

84. Trzeciak HI, Grzesik J, Bortel M, et al. Behavioral effects of long-term exposure to magnetic fields in rats. *Bioelectromagnetics* 1993;**14**(4)**:**287-97.

85. Nakagawa M, Matsuda Y. A strong static-magnetic field alters operant responding by rats. *Bioelectromagnetics* 1988;**9**(1)**:**25-37.

86. Weissman JL, Curtin HD, Hirsch BE, Hirsch WL, Jr. High signal from the otic labyrinth on unenhanced magnetic resonance imaging. *Am J Neuroradiol* 1992;**13**(4)**:**1183-7.

87. Nolte CM, Pittman DW, Kalevitch B, Henderson R, Smith JC. Magnetic field conditioned taste aversion in rats. *Physiol Behav* 1998;**63**(4)**:**683-8.

88. Snyder DJ, Jahng JW, Smith JC, Houpt TA. c-Fos induction in visceral and vestibular nuclei of the rat brain stem by a 9.4 T magnetic field. *Neuroreport* 2000;**11**(12)**:**2681-5.

89. Houpt TA, Pittman DW, Barranco JM, Brooks EH, Smith JC. Behavioral effects of high-strength static magnetic fields on rats. *J Neurosci* 2003;**23**(4)**:**1498-505.

90. Lockwood DR, Kwon B, Smith JC, Houpt TA. Behavioral effects of static high magnetic fields on unrestrained and restrained mice. *Physiol Behav* 2003;**78**(4-5)**:**635-40.

91. Levine RL, Dooley JK, Bluni TD. Magnetic field effects on spatial discrimination and melatonin levels in mice. *Physiol Behav* 1995;**58**(3)**:**535-7.

92. Saunders R. Static magnetic fields: animal studies. *Prog Biophys Mol Biol* 2005;**87**(2-3)**:**225-39.

93. Brandt T, Strupp M. General vestibular testing. *Clin Neurophysiol* 2005;**116**(2)**:**406-26.

94. Reason G, Brand J. Motion Sickness. London: Academic Press, 1975.

95. Nachum Z, Gordon CR, Shahal B, Spitzer O, Shupak A. Active high-frequency vestibulo-ocular reflex and seasickness susceptibility.

Laryngoscope 2002;**112**(1)**:**179-82.

96. Graybiel A. Structural elements in the concept of motion sickness. *Aerosp Med* 1969;**40**(4)**:**351-67.
97. Stoffregen TA, Riccio GE. An ecological theory of orientation and the vestibular system. *Psychol Rev* 1988;**95**(1)**:**3-14.
98. Gresty MA, Bronstein AM, Brandt T, Dieterich M. Neurology of otolith function. Peripheral and central disorders. *Brain* 1992;**115 (Pt 3):**647-73.
99. Brodal P. The Central Nervous System. Structure and function. 3rd ed. New York: Oxford University Press, 2004.
100. Evans JA, Savitz DA, Kanal E, Gillen J. Infertility and pregnancy outcome among magnetic resonance imaging workers. *J Occup Med* 1993;**35**(12)**:**1191-5.
101. Mur JM, Wild P, Rapp R, Vautrin JP, Coulon JP. Demographic evaluation of the fertility of aluminium industry workers: influence of exposure to heat and static magnetic fields. *Hum Reprod* 1998;**13**(7)**:**2016-9.
102. Irgens A, Kruger K, Skorve AH, Irgens LM. Male proportion in offspring of parents exposed to strong static and extremely low-frequency electromagnetic fields in Norway. *Am J Ind Med* 1997;**32**(5)**:**557-61.
103. Tuschl H, Neubauer G, Schmid G, Weber E, Winker N. Occupational exposure to static, ELF, VF and VLF magnetic fields and immune parameters. *Int J Occup Med Environ Health* 2000;**13**(1)**:**39-50.
104. Kheifets LI, Afifi AA, Buffler PA, Zhang ZW. Occupational electric and magnetic field exposure and brain cancer: a meta-analysis. *J Occup Environ Med* 1995;**37**(12)**:**1327-41.
105. Kheifets LI, Afifi AA, Buffler PA, Zhang ZW, Matkin CC. Occupational electric and magnetic field exposure and leukemia. A meta-analysis. *J Occup Environ Med* 1997;**39**(11)**:**1074-91.
106. IARC Monographs Vol. 80. Non-ionizing Radiation, Part 1: Static and Extremely Low Frequency (ELF) Electric and Magnetic Fields: IARC, 2002.
107. White RF, Proctor SP. Research and clinical criteria for development of neurobehavioral test batteries. *J Occup Med* 1992;**34**(2)**:**140-8.
108. Spurgeon A. The use of neurobehavioural test batteries for research, diagnosis and screening: methodological aspects. *Toxicol Lett*

1995;**82-83:**191-5.

109. Lucchini R, Albini E, Benedetti L, Alessio L. Neurobehavioral science in hazard identification and risk assessment of neurotoxic agents—what are the requirements for further development? *Int Arch Occup Environ Health* 2005;**78**(6)**:**427-37.

110. Spurgeon A. Current approaches to neurobehavioural testing in occupational health. *Occup Environ Med* 1996;**53**(11)**:**721-5.

111. Lezak M, Howieson D, Loring D, Hannay H, JS. F. A compendium of tests and assessment techniques. In: Lezak M, ed. Neuropsychological Assessment. 4 ed. New York: Oxford University Press, 2004.

112. Hudnell HK, Otto DA, House DE. The influence of vision on computerized neurobehavioral test scores: a proposal for improving test protocols. *Neurotoxicol Teratol* 1996;**18**(4)**:**391-400.

113. Wesnes K, Pincock C. Practice effects on cognitive tasks: a major problem? *Lancet Neurol* 2002;**1**(8)**:**473.

114. Salinsky MC, Storzbach D, Dodrill CB, Binder LM. Test-retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12-16-week period. *J Int Neuropsychol Soc* 2001;**7**(5)**:**597-605.

115. Beglinger LJ, Gaydos B, Tangphao-Daniels O, et al. Practice effects and the use of alternate forms in serial neuropsychological testing. *Arch Clin Neuropsychol* 2005;**20**(4)**:**517-29.

116. McClelland G. The effects of practice on measures of performance. *Human Psychopharmacol* 1987;**210:**109-118.

117. Collie A, Maruff P, Darby DG, McStephen M. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 2003;**9**(3)**:**419-28.

118. Benedict RH, Zgaljardic DJ. Practice effects during repeated administrations of memory tests with and without alternate forms. *J Clin Exp Neuropsychol* 1998;**20**(3)**:**339-52.

119. Ivnik R, Smith G, Malec J, al. e. Long-term stability and intercorrelations of cognitive abilities in older persons. *Psychological Assessment* 1995;**7:**155-161.

120. Ivnik RJ, Smith GE, Lucas JA, et al. Testing normal older people three or four times at 1- to 2-year intervals: defining normal

variance. *Neuropsychology* 1999;**13**(1)**:**121-7.

121. Theisen ME, Rapport LJ, Axelrod BN, Brines DB. Effects of practice in repeated administrations of the Wechsler Memory Scale Revised in normal adults. *Assessment* 1998;**5**(1)**:**85-92.
122. FDA. Guidance for industry and FDA staff. Criteria for significant risk investigations of magnetic resonance diagnostic devices. (CDRH) , Rockville, MD, 2003.
123. Lovsund P, Oberg PA, Nilsson SE. Influence on vision of extremely low frequence electromagnetic fields. Industrial measurements, magnetophosphene studies volunteers and intraretinal studies in animals. *Acta Ophthalmol (Copenh)* 1979;**57**(5)**:**812-21.
124. Innis NK, Ossenkopp KP, Prato FS, Sestini E. Behavioral effects of exposure to nuclear magnetic resonance imaging: II. Spatial memory tests. *Magn Reson Imaging* 1986;**4**(4)**:**281-4.
125. Ossenkopp KP, Innis NK, Prato FS, Sestini E. Behavioral effects of exposure to nuclear magnetic resonance imaging: I. Open-field behavior and passive avoidance learning in rats. *Magn Reson Imaging* 1986;**4**(4)**:**275-80.
126. Messmer JM, Porter JH, Fatouros P, Prasad U, Weisberg M. Exposure to magnetic resonance imaging does not produce taste aversion in rats. *Physiol Behav* 1987;**40**(2)**:**259-61.
127. Muller-Miny H, Erber D, Moller H, Muller-Miny B, Bongartz G. Is there a hazard to health by mercury exposure from amalgam due to MRI? *J Magn Reson Imaging* 1996;**6**(1)**:**258-60.
128. Baker EL, Letz R. Neurobehavioral testing in monitoring hazardous workplace exposures. *J Occup Med* 1986;**28**(10)**:**987-90.
129. WHO. World Health Organization (WHO)-Recommended Neurobehavioral Core Test Battery Operational Guide. Geneva: WHO, 1986.
130. Muijser H, Geuskens RB, Hooisma J, Emmen HH, Kulig BM. Behavioral effects of exposure to organic solvents in carpet layers. *Neurotoxicol Teratol* 1996;**18**(4)**:**455-62.
131. McCulloch C, Searle S. Longitudinal data. Generalized, linear, and mixed models. New York: John Wiley & Sons Inc, 2001.
132. Ghosh D, Deisher TA, Ellsworth JL. Statistical methods for analyzing repeated measures.*J Pharmacol Toxicol Methods* 1999;**42**(3)**:**157-62.

133. Snijders T, Bosker R. Multilevel Analysis: An introduction to basic and advanced multilevel modeling. London: Sage Publications Ltd, 1999.
134. Berglund A, Bergdahl J, Hansson Mild K. Influence of low frequency magnetic fields on the intra-oral release of mercury vapor from amalgam restorations. *Eur J Oral Sci* 1998;**106**(2 Pt 1)**:**671-4.
135. Kaibara T, Saunders JK, Sutherland GR. Advances in mobile intraoperative magnetic resonance imaging. *Neurosurgery* 2000;**47**(1)**:**131-7; discussion 137-8.
136. Anonymous. Magnetic Resonance and intervention/therapy. Application of MR technology to endovascular interventions in an XMR Suite. *MedicaMundi* 2002;**46**(3).
137. Anger WK, Liang YX, Nell V, et al. Lessons learned—15 years of the WHO-NCTB: a review. *Neurotoxicology* 2000;**21**(5)**:**837-46.
138. Lezak M, Howieson D, Loring D, Hannay H, JS. F. A compendium of tests and assessment techniques. In: Lezak M, ed. Neuropsychological Assessment. 3rd ed. New York: Oxford University Press, 1995: 333-806.
139. Kennedy RS, Dunlap WP. Assessment of the Vistech contrast sensitivity test for repeated-measures applications. *Optom Vis Sci* 1990;**67**(4)**:**248-51.
140. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;**133**(2)**:**144-53.
141. Checkoway H. Case-crossover designs in occupational health. *Occup Environ Med* 2004;**61**(12)**:**953-4.
142. Varadhan R, Frangakis CE. Revealing and addressing length bias and heterogeneous effects in frequency case-crossover studies. *Am J Epidemiol* 2004;**159**(6)**:**596-602.
143. Glowinski A, Adam G, Bucker A, Neuerburg J, van Vaals JJ, Gunther RW. Catheter visualization using locally induced, actively controlled field inhomogeneities. *Magn Reson Med* 1997; **38**(2)**:**253-8.
144. Shellock FG. Reference manual for magnetic resonance safety: 2002 edition. Salt Lake City, Utah: Amirsys, Inc., 2002.
145. Kanal E, Shellock FG, Talagala L. Safety considerations in MR imaging. *Radiology* 1990;**176**(3)**:**593-606.

146. Kangarlu A, Shellock FG. Aneurysm clips: evaluation of magnetic field interactions with an 8.0 T MR system. *J Magn Reson Imaging* 2000;**12**(1)**:**107-11.

147. Martin ET, Coman JA, Shellock FG, Pulling CC, Fair R, Jenkins K. Magnetic resonance imaging and cardiac pacemaker safety at 1.5-Tesla. *J Am Coll Cardiol* 2004;**43**(7)**:**1315-24.

148. Schneider JP, Schulz T, Schmidt F, et al. Gross-total surgery of supratentorial low-grade gliomas under intraoperative MR guidance. *Am J Neuroradiol* 2001;**22**(1)**:**89-98.

149. Nour SG, Lewin JS, Gutman M, et al. Percutaneous MR imaging-guided radiofrequency interstitial thermal ablation of tongue base in porcine models: implications for obstructive sleep apnea syndrome. *Radiology* 2004;**230**(2)**:**359-68.

150. Gaffey CT, Tenforde TS. Alterations in the rat electrocardiogram induced by stationary magnetic fields. *Bioelectromagnetics* 1981;**2**(4)**:**357-70.

151. Bloom B. Taxonomy of educational objectives: The classification of educational goals: Handbook I, cognitive domain. New York: Addison Wesley Publishing Company, 1956.

152. High WB, Sikora J, Ugurbil K, Garwood M. Subchronic in vivo effects of a high static magnetic field (9.4 T) in rats. *J Magn Reson Imaging* 2000;**12**(1)**:**122-39.

153. Nakahara T, Yaguchi H, Yoshida M, Miyakoshi J. Effects of exposure of CHO-K1 cells to a 10-T static magnetic field. *Radiology* 2002;**224**(3)**:**817-22.

154. Shellock FG, Crues JV. Temperature, heart rate, and blood pressure changes associated with clinical MR imaging at 1.5 T. *Radiology* 1987;**163**(1)**:**259-62.

155. Shellock FG, Crues JV. Temperature changes caused by MR imaging of the brain with a head coil. *Am J Neuroradiol* 1988;**9**(2)**:**287-91.

156. Barfuss H, Fischer H, Hentschel D, Ladebeck R, Vetter J. Whole-body MR imaging and spectroscopy with a 4-T system. *Radiology* 1988;**169**(3)**:**811-6.

157. Barfuss H, Fischer H, Hentschel D, et al. In vivo magnetic resonance imaging and spectroscopy of humans with a 4 T whole-body magnet. *NMR Biomed* 1990;**3**(1)**:**31-45.

158. Kinouchi Y, Yamaguchi H, Tenforde TS. Theoretical analysis of

magnetic field interactions with aortic blood flow. *Bioelectromagnetics* 1996;**17**(1)**:**21-32.

159. Schulz T, Trobs RB, Schneider JP, et al. Pediatric MR-guided interventions. *Eur J Radiol* 2005;**53**(1)**:**57-66.
160. Quick HH, Zenge MO, Kuehl H, et al. Interventional magnetic resonance angiography with no strings attached: wireless active catheter visualization. *Magn Reson Med* 2005;**53**(2)**:**446-55.
161. Erhard P, Chen W, Lee J, Ugurbil K. A study of effects reported by subjects at high magnetic fields. Soc Magn Reson 1995.
162. Rothman K, Greenland S. Types of epidemiologic studies. In: Rothman K, Greenland S, eds. Modern Epidemiology. 2 ed. Philadelphia: Lippincott, Williams & Wilkins, 1998: 752.
163. Gilmore GC. Scoring of contrast sensitivity on Vistech charts. *J Neurol Sci* 2002;**205**(1)**:**85.
164. Rapport LJ, Axelrod BN, Theisen ME, Brines DB, Kalechstein AD, Ricker JH. Relationship of IQ to verbal learning and memory: test and retest. *J Clin Exp Neuropsychol* 1997;**19**(5)**:**655-66.
165. Sweetland J, Kertesz A, Prato FS, Nantau K. The effect of magnetic resonance imaging on human cognition. *Magn Reson Imaging* 1987;**5**(2)**:**129-35.
166. Cavin I, Gowland P, Glover P, Bowtell R. Sensory Experiences of Healthy Volunteers exposed to Ultra high MRI Static Magnetic Fields. Proceedings ISMRM Workshop on MRI Safety: Update, Practical Information and Future Implications 2005, McLean, Virginia, USA.
167. Bandettini P, Petridou N, Bodurka J. Direct Detection of Neuronal Activity with MRI: Fantasy, Possibility, or Reality? *Applied Magnetic Resonance* 2005;**29**(1)**:**65-88.
168. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000;**21:**193-221.
169. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;**1**(1)**:**43-6.
170. Cleophas TJ. Clinical trials: Renewed attention to the interpretation of the P values—review. *Am J Ther* 2004;**11**(4)**:**317-22.
171. Kroeker G, Parkinson D, Vriend J, Peeling J. Neurochemical effects of static magnetic field exposure. *Surg Neurol* 1996;**45**(1)**:**62-6.
172. Binhi VN, Blackman CF. Analysis of the structure of magnetic fields

that induced inhibition of stimulated neurite outgrowth. *Bioelectromagnetics* 2005;**26**(8)**:**684-9.

173. Binhi VN, Savin AV. Molecular gyroscopes and biological effects of weak extremely low-frequency magnetic fields. *Phys Rev E Stat Nonlin Soft Matter Phys* 2002;**65**(5 Pt 1)**:**051912.
174. Redelmeier DA, Tibshirani RJ. Interpretation and bias in case-crossover studies. *J Clin Epidemiol* 1997;**50**(11)**:**1281-7.
175. Sugiura M, Kawashima R, Nakagawa M, et al. Correlation between human personality and neural activity in cerebral cortex. *Neuroimage* 2000;**11**(5 Pt 1)**:**541-6.
176. Cook CM, Thomas AW, Prato FS. Human electrophysiological and cognitive effects of exposure to ELF magnetic and ELF modulated RF and microwave fields: a review of recent studies. *Bioelectromagnetics* 2002;**23**(2)**:**144-57.
177. Swartzman LC, Burkell J. Expectations and the placebo effect in clinical drug trials: why we should not turn a blind eye to unblinding, and other cautionary notes. *Clin Pharmacol Ther* 1998;**64**(1)**:**1-7.
178. Peretz C, Goren A, Smid T, Kromhout H. Application of mixed-effects models for exposure assessment. *Ann Occup Hyg* 2002;**46**(1)**:**69-77.
179. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. *Stat Med* 1998;**17**(11)**:**1261-91.
180. Singer J. Using PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *J Educ Behav Stat* 1998;**24**(4)**:**323-355.
181. Whittington CJ, Podd JV. Human performance and physiology: a statistical power analysis of ELF electromagnetic field research. *Bioelectromagnetics* 1996;**17**(4)**:**274-8.
182. Whittington CJ, Podd JV, Rapley BR. Acute effects of 50 Hz magnetic field exposure on human visual task and cardiovascular performance. *Bioelectromagnetics* 1996;**17**(2)**:**131-7.
183. Kazantzis N, Podd J, Whittington C. Acute effects of 50 Hz, 100 microT magnetic field exposure on visual duration discrimination at two different times of the day. *Bioelectromagnetics*

1998;**19**(5)**:**310-7.

184. Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol* 2001;**54**(4)**:**343-9.
185. Ludbrook J. On making multiple comparisons in clinical and experimental pharmacology and physiology. *Clin Exp Pharmacol Physiol* 1991;**18**(6)**:**379-92.
186. Gordi T, Khamis H. Simple solution to a common statistical problem: interpreting multiple tests. *Clin Ther* 2004;**26**(5)**:**780-6.
187. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995;**310**(6973)**:**170.
188. Curran-Everett D. Multiple comparisons: philosophies and illustrations. *Am J Physiol Regul Integr Comp Physiol* 2000;**279**(1)**:**R1-8.
189. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998;**316**(7139)**:**1236-8.
190. Feise RJ. Do multiple outcome measures require p-value adjustment? *Med Res Methodol* 2002;**2:**8.
191. Greenwald AG, Gonzalez R, Harris RJ, Guthrie D. Effect sizes and p values: what should be reported and what should be replicated? *Psychophysiology* 1996;**33**(2)**:**175-83.
192. Cavin I, Gowland P, Glover P, et al. Static B_0 Field Monitoring at 3 Tesla and 7 Tesla using an MRI portable Dosemeter. Proceedings ISMRM Workshop on MRI Safety: Update, Practical Information and Future Implications 2005.
193. Cavagnetto F, Prati P, Ariola V, et al. A personal dosimeter prototype for static magnetic fields. *Health Phys* 1993;**65**(2)**:**172-7.
194. Bracken TD. Exposure assessment for power frequency electric and magnetic fields. *Am Ind Hyg Assoc J* 1993;**54**(4)**:**165-77.
195. Symanski E, Sallsten G, Chan W, Barregard L. Heterogeneity in sources of exposure variability among groups of workers exposed to inorganic mercury. *Ann Occup Hyg* 2001;**45**(8)**:**677-87.
196. Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. Individual-based and group-based occupational exposure assessment: some equations to evaluate different strategies. *Ann Occup Hyg* 1998;**42**(2)**:**115-9.
197. Burstyn I, Kim HM, Cherry N, Yasui Y. Metamodels of bias in Cox proportional-hazards and logistic regressions with heteroscedastic

measurement error under group-level exposure assessment. *Ann Occup Hyg* 2005.

198. Sauleau EA, Wild P, Hours M, Leplay A, Bergeret A. Comparison of measurement strategies for prospective occupational epidemiology. *Ann Occup Hyg* 2003;**47**(2)**:**101-10.
199. Gordon CR, Spitzer O, Doweck I, Shupak A, Gadoth N. The vestibulo-ocular reflex and seasickness susceptibility. *J Vestib Res* 1996;**6**(4)**:**229-33.
200. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A, Eberle L. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalogr Clin Neurophysiol* 1989;**74**(6)**:**458-62.
201. Priori A, Bertolasi L, Rothwell JC, Day BL, Marsden CD. Some saccadic eye movements can be delayed by transcranial magnetic stimulation of the cerebral cortex in man. *Brain* 1993;**116 (Pt 2):**355-67.
202. Kammer T, Nusseck HG. Are recognition deficits following occipital lobe TMS explained by raised detection thresholds? *Neuropsychologia* 1998;**36**(11)**:**1161-6.
203. Miyawaki Y, Okada M. A network model of perceptual suppression induced by transcranial magnetic stimulation. *Neural Comput* 2004;**16**(2)**:**309-31.
204. Mottaghy FM. Interfering with working memory in humans. *Neuroscience* 2005; .
205. Adair RK. Simple neural networks for the amplification and utilization of small changes in neuron firing rates. *Proc Natl Acad Sci U S A* 2001;**98**(13)**:**7253-8.
206. Saunders RD. Rapporteur report: weak field interactions in the central nervous system. *Radiat Prot Dosimetry* 2003;**106**(4)**:**357-61.
207. Kammer T. Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: their topographic relationship. *Neuropsychologia* 1999;**37**(2)**:**191-8.
208. Terao Y, Fukuda H, Ugawa Y, et al. Visualization of the information flow through human oculomotor cortical regions by transcranial magnetic stimulation. *J Neurophysiol* 1998;**80**(2)**:**936-46.
209. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell AP, Eberle

L. Unmasking human visual perception with the magnetic coil and its relationship to hemispheric asymmetry. *Brain Res* 1993;**605**(2)**:**312-6.

210. Amassian VE, Maccabee PJ, Cracco RQ, Cracco JB, Rudell AP, Eberle L. Measurement of information processing delays in human visual cortex with repetitive magnetic coil stimulation. *Brain Res* 1993;**605**(2)**:**317-21.

211. Baddeley A. The episodic buffer: a new component of working memory? *Trends Cogn Sci* 2000;**4**(11)**:**417-423.

212. Baddeley AD, Hitch GJ. Development of working memory: should the Pascual-Leone and the Baddeley and Hitch models be merged? *J Exp Child Psychol* 2000;**77**(2)**:**128-37.

213. Baddeley AD. Is working memory still working? *Am Psychol* 2001;**56**(11)**:**851-64.

214. Mull BR, Seyal M. Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. *Clin Neurophysiol* 2001;**112**(9)**:**1672-5.

215. WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York: WHO, 1948.

216. Faragher EB, Cass M, Cooper CL. The relationship between job satisfaction and health: a meta-analysis. *Occup Environ Med* 2005;**62**(2)**:**105-12.

217. Costa G, Akerstedt T, Nachreiner F, et al. Flexible working hours, health, and well-being in Europe: some considerations from a SALTSA project. *Chronobiol Int* 2004;**21**(6)**:**831-44.

218. Ising H, Kruppa B. Health effects caused by noise: evidence in the literature from the past 25 years. *Noise Health* 2004;**6**(22)**:**5-13.

219. Keevil SF, Gedroyc W, Gowland P, et al. Electromagnetic field exposure limitation and the future of MRI. *Br J Radiol* 2005;**78**(935)**:**973.

220. Engels H. Minimum Health and Safety Requirements for EMF exposure: Consequences for the MR Community. Proceedings ISMRM Workshop on MRI Safety: Update, Practical Information and Future Implications 2005.

221. Shupak A, Kerem D, Gordon C, Spitzer O, Mendelowitz N, Melamed Y. Vestibulo-ocular reflex as a parameter of seasickness

susceptibility. *Ann Otol Rhinol Laryngol* 1990;**99**(2 Pt 1)**:**131-6.

222. Gordon CR, Ben-Aryeh H, Spitzer O, et al. Seasickness susceptibility, personality factors, and salivation. *Aviat Space Environ Med* 1994;**65**(7)**:**610-4.

223. Gordon CR, Jackman Y, Ben-Aryeh H, et al. Salivary secretion and seasickness susceptibility. *Aviat Space Environ Med* 1992;**63**(5)**:**356-9.

224. Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. *Brain Res Bull* 1998;**47**(5)**:**507-16.

Appendix

Methods Pooled Pursuit Aiming II and VISTECH 6000™ analyses

The Pursuit Aiming II test and the VISTECH 6000™ test were used to assess eye-hand coordination and visual contrast sensitivity respectively, in all three studies assessing neurobehavioral performance during exposure to magnetic gradient fields (chapters 3, 5 and 6). As described, statistical significant results was found for eye-hand coordination at the $P < 0.10$ level in these studies, while a significant reduction in visual contrast sensitivity was only found in the first study (chapter 3). In the two subsequent studies (chapters 5 and 6) performance was not significantly reduced at $P < 0.10$, but the differences in absolute test performance in these studies did suggest a similar effect.

Therefore, we conducted a pooled analysis of these test results for. Only measurements were additional head movements were done were used in the analyses, resulting in a final study population of 64 persons with two (1.5 T study) or three repeated measurements per person. The estimates of average static magnetic field intensities presented have been used in the linear mixed effects model of the pooled analysis, resulting in the following model to analyze the results:

$$Y_{ij}= \beta_{00} + \beta_{10}x_{ij} + \beta_{20}x_{ij} + \beta_{30}x_{ij} + U_{0j} + R_{ij}$$

where:

Y_{ij}= performance of a volunteer at the Pursuit Aiming II-test or at the VISTECH test ($\log_{10}$ transformed).

β_{00}= intercept, or underlying mean test performance

β_{10}= average change in test performance caused by exposure (0 Tesla, 0.6 T, 0.7 T, 0.8 T, 1.0 T and 1.6 T, respectively)

β_{20}= adjustment for an average difference between the studies

β_{30}= adjustment for practice effect

U_{0j}= random intercept adjustment to account for natural heterogeneity in test performance between volunteers ($\sim N(0,\sigma^2_{\text{between-subject}})$

R_{ij}= residual, or within-subject variance ($\sim N(0,\sigma^2_{\text{within-subject}})$

The determinant to identify each study (β_{20}) can be regarded as a proxy for a number of factors that are different between the study; differences in natural test performance between the study populations in all studies, the exact location in the stray field and the resulting exposure

to B_0 and dB_0/dx; differences in the additional movements performed during exposure, and thus differences in dB_0/dt exposure.
The results of these analyses are presented in Table 1, and graphically for the VISTECH 6000™-test in Figure 1, in the General Discussion (chapter 7).

AFFILIATION OF CONTRIBUTORS

Donald W. Chakeres: Department of Radiology, College of Medicine and Public Health, Ohio State University Hospital, The Ohio State University, Columbus, OH, United States.

Hinkelien van Drooge: Environmental and Occupational Health Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
Koninklijke Marine, Den Helder, The Netherlands.

Hans Engels: Philips Medical Systems, Best, The Netherlands.

Paul Glover: Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, The University of Nottingham, Nottingham, United Kingdom

Penny Gowland: Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, The University of Nottingham, Nottingham, United Kingdom

Hans Kromhout: Environmental and Occupational Health Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands.

Tobias Stevens: Environmental and Occupational Health Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands.

Alan Sunderland: School of Psychology, The University of Nottingham, Nottingham, United Kingdom

Berna van Wendel de Joode: Central American Institute for Studies on Toxic Substances (IRET), National University, Heredia, Costa Rica.
Environmental and Occupational Health Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands.

TABLES

FIGURES

SUMMARY

Intensity and duration of occupational exposure to static magnetic fields (SMF) from magnetic resonance imaging (MRI) systems is likely to increase in the near future. The main reasons for this are a drive towards the development and use of stronger magnets in clinical practice, research and industry and an increase in the number of interventional applications and procedures involving MRI in clinical practice. People working routinely with these systems have reported a number of symptoms related to their presence in the inhomogeneous static magnetic fields (the stray field) surrounding MRI scanners. In this thesis these symptoms, as well as neurobehavioral performance, have been studied in relation to exposure to stray fields from MRI systems.

In an observational study among engineers manufacturing 0.5, 1.0 and 1.5 Tesla systems, experienced symptoms and neurobehavioral performance were assessed and compared to that of employees from a reference department at the same company. Average exposure to static magnetic fields of these workers during several standard procedures was estimated at 25.9 mT/8h for working with a 1.0 T system and at 40.4 mT/8h for a 1.5 T system. Vertigo, metal taste, and concentration problems were more often reported by workers of the MRI-manufacturing department than in the reference department, and were dependent on intensity and duration of exposure. All symptoms, except for headaches, were more frequently reported by engineers who moved through the magnetic stray field more rapidly than others.

Mercury levels in urine samples were determined to assess whether frequently reported metallic taste during presence in strong magnetic fields could be caused by release of amalgam from teeth fillings. No correlation was found with exposure and most likely experiencing a metal taste is being caused by “random” excitation of nerve tissue in the mouth or to electrolysis of metallic fillings.

In addition, a series of experimental studies on company or naive volunteers were conducted to quantitatively assess acute and transient effects on neurobehavioral performance during exposure to static magnetic stray fields from MRI scanners up to 7.0 Tesla. Acute adverse neurobehavioral effects could already be measured during exposure to

approximately 600 mT, but no significant changes in performance were found after exposure had ended. The visual sensory domain (visual tracking and visual contrast sensitivity) and the cognitive-motor (Pursuit Aiming II (PAII) and adapted line-bisection (LB)) domain were affected by exposure to magnetic fields. Performance at visual tracking (range -3.1 to -1.3%/100mT) and eye-hand coordination tasks (range $\mathrm{PAII}_{\mathrm{accuracy}}$=-0.10 to -0.56%/100mT and range LB=-0.17%/100mT) depended on intensity of exposure.

Additional pooled analyses showed that accuracy, and not speed, at the PAII tests was affected (-0.10%/100mT). Visual contrast sensitivity at a spatial frequency of 6 cycles per degree was slightly decreased by exposure (-0.74%), but an exposure-response relation was not found. These effects were most likely related to movement in the stray fields, and associated exposure to a time-varying magnetic field. Performances at tests assessing visuo-verbal interference, verbal attention, visuo-motor speed, dexterity and visual scanning were not affected. It remained inconclusive whether working memory was affected, but most likely effects are not significant enough to confound results from functional MRI studies.

Presumably, the reported symptoms are similar to motion sickness-like symptoms and result from variance in information presented to the vestibular system and resulting erogenous reactions in the vestibulo-ocular reflex.

The results presented in this thesis implicate that people regularly working in the vicinity of MRI scanners, such as engineers in MR manufacturing or members of operating teams involved in interventional procedures applying MRI, should be made consciously aware of these potential hazards and should limit their movement speed and presence in the stray fields of MRI scanners as much as possible. It remains unknown what the measured neurobehavioral effects mean for functional capacity in the occupational setting, since this relation has not been studied in this thesis.

In spite of rapid new developments in MRI systems and applications existing gaps in knowledge about the effects of occupational exposure to magnetic stray fields of MRI systems are evident. A lack of validated and commercially available personal dosimeters to measure exposure to strong static, spatial gradient and time-varying magnetic fields however prohibits studies evaluating occupational exposure to these fields as well as standard setting. Finally, despite the fact that studies presented in this thesis point at transient neurobehavioral effects in the visual sensory and visuomotor domains, independent replicate studies are needed to confirm these findings.

SAMENVATTING

De blootstellingsintensiteit en –duur aan statische magneetvelden van magnetic resonance imaging (MRI) systemen zal naar alle waarschijnlijkheid in de nabije toekomst toenemen. De belangrijkste redenen hiervoor zijn de ontwikkeling en het gebruik van steeds sterkere magneten in de klinische praktijk, wetenschap en industrie en een toename in het aantal interventionele procedures in de kliniek waarbij MRI wordt gebruikt. Werknemers die regelmatig met deze systemen werken rapporteren echter een aantal gezondsklachten die over het algemeen gerelateerd worden aan hun aanwezigheid in de inhomogene, statische magneetvelden (strooivelden) die MRI scanners omgeven. In dit proefschrift is de frequentie van deze gerapporteerde gezondheidsklachten, alsmede prestatie bij verschillende neuropsycho-logische testen om effecten quantitatief te kunnen analyseren, in relatie tot blootstelling aan strooivelden van deze MRI systemen bestudeerd.

Gerapporteerde gezondheidklachten en prestatie tijdens neuropsychologische testen zijn geanalyseerd bij technici die 0.5, 1.0 en 1.5 Tesla systemen ontwikkelen en bij een controlegroep van een andere afdeling binnen hetzelfde bedrijf. De gemiddelde blootstelling aan statische magneetvelden van deze werknemers tijdens tijdens het uitvoeren van verschillende standaardprocedures werd geschat op 25.9 mT/8uur bij een 1.0 T systeem en op 40.4 mT/8u bij een 1.5 T systeem. Duizeligheid, metaalsmaak, en concentratieproblemen werden vaker gerapporteerd op de MRI afdeling dan op de controle afdeling, en was gerelateerd aan de intensiteit en de duur van de blootstelling. Behalve hoofdpijn werden alle gezondheidsklachten vaker gerapporteerd door de werknemers die zich sneller door de strooivelden bewogen dan door diegene die hun werk langzamer uitvoerden.

Om te analyseren of de gerapporteerde metaalsmaak werd veroorzaakt door een afgifte van amalgaam uit vullingen door blootstelling aan een sterk magneetveld werd de kwik concentratie in de urine van werknemers bepaald. Er werd echter geen correlatie gevonden met de blootstelling. Meer waarschijnlijke oorzaken zijn een “random” prikkeling van gevoelig zenuwweefsel in de mond, of door elektrolyse van de vullingen.

In een serie experimentele studies bij bedrijfsvrijwilligers en bij vrijwilligers uit de algemene populatie werden acute, tijdelijke effecten op de prestatie op neurolopsychologische testen tijdens blootstelling aan strooivelden van MRI scanners tot 7 Tesla kwantitatief gemeten. Hoewel al bij een blootstelling aan ongeveer 600mT een vermindering van de prestatie op sommige testen kon worden gemeten, konden geen effecten meer worden aangetoond na beeindiging van de blootstelling.

Het visuele (visual tracking en visuele contrastgevoeligheid) en het cognitief-motorisch (Pursuit Aiming II (PAII) en de aangepaste line-bisection test (LB)) domein werden beinvloed door de blootstelling. Prestatie op de visual tracking (-3.1 tot -1.3% per 100mT blootstelling) en de oog-hand coordinatie testen ($\text{PAII}_{\text{precisie}}$ = -0.10 tot -0.56% per 100mT en LB=-0.17%/100mT) was gerelateerd aan de intensiteit van de blootstelling. Een gezamelijke analyse van de resultaten van de verschillende studies liet zien dat precisie, en niet de snelheid, tijdens de PAII test negatief werd beinvloed door de blootstelling (-0.10%/100mT). Visuele contrastgevoeligheid werd lichtelijk beinvloed door blootstelling aan het statische magneetveld bij een ruimtelijk contrast van 6 cpd (-0.74%), maar een blootstellings-effect relatie werd niet gevonden. Zeer waarschijnlijk worden deze effecten veroorzaakt door het bewegen in inhomogene magnetische strooivelden en de daarmee geassocieerde veranderingen van het magneetveld in de tijd. Effecten op de prestatie bij testen die visueel-verbale interferentie, concentratievermogen, visueel-motorische snelheid, behendigheid en visuele scanvermogen testen werden niet aangetoond. Op basis van de tegenstrijdige resultaten bij testen voor het werkgeheugen kunnen er geen conclusies worden getrokken over beinvloeding van dit domein door blootstelling aan magnetische strooivelden. De resultaten suggereren echter wel dat als het werkgeheugen inderdaad beinvloed zou worden, deze effecten niet groot genoeg zijn om de resulaten van functional MRI studies te kunnen verstoren.

De aangetoonde effecten zijn vergelijkbaar met symptomen die bij bewegingsziekte worden ervaren, en worden waarschijnlijk veroorzaakt door afwijkingingen in de informatie naar het vestibulaire systeem en de resulterende fouten in de vestibulo-oculaire reflex.

De resultaten van de studies in dit proefschrift suggereren dat werknemers die regelmatig in de buurt van MRI scanners werken, zoals

MR-technici en operatie teams tijdens interventionele procedures met MRI, voorgelicht moeten worden over de relatie tussen blootstelling aan magnetische strooivelden en het potentieel ervaren van verschillende gezondheidsklachten en eventuele effecten op de uitvoering van hun werk. Verder zouden bewust zowel hun snelheid in het magneetveld, als de duur van hun aanwezigheid in het strooiveld, zoveel mogelijk moeten worden gelimiteerd. Aangezien de relatie tussen prestatie op neuropsychologische testen en het dagelijks functioneren nog niet goed is onderzocht blijft het echter nog onduidelijk in hoeverre de gevonden effecten de prestatie op de werkvloer kunnen beinvloeden.

Ondanks de snelle ontwikkeling van nieuwe MRI systemen en toepassingen, is er nog veel onbekend over de effecten van blootstelling aan magnetische strooivelden van MRI scanners. Door het ontbreken van gevalideerde, commercieel verkrijgbare, persoonlijke dosismeters om blootstelling aan sterke statische magneetvelden, ruimtelijke gradientvelden en tijdsafhankelijke magneetvelden te meten, blijft het ingewikkeld effecten van blootstelling aan deze velden goed te analyseren, alsmede adequate blootstellingslimieten vast te stellen. Ondanks dat met name de resultaten gepresenteerd in dit proefschrift wijzen in de richting van tijdelijke beinvloeding van het visuele en het visuele-motot domein, is er dringende behoefte aan onafhankelijke herhaling van deze studies om de resultaten te kunnen bevestigen.

ABOUT THE AUTHOR

Frank Gérard de Vocht was born in Boxmeer, The Netherlands on January 15th, 1978. He completed secondary school (het Elzendaalcollege) in 1996 and started the M.Sc. program of Environmental Science at Wageningen University (WUR).

After internships at the Institute Municipal d'Investigació Médica (IMIM) in Barcelona, Harvard School of Public Health in Boston and the National Cancer Institute in Bethesda, he obtained his Master title in 2002.

He started working at the Institute for Risk Assessment Sciences (IRAS) at Utrecht University where he was involved in a series of studies related to symptoms and effects on neurobehavioral performance of exposure to strong magnetic fields. In addition, he was involved in an internatiomal multi-centre study on historical exposures to chemicals in the European rubber manufacturing industry (European Union Concerted Action EXASRUB).

At present, he is also involved in the exposure assessment for an international multi-centre nested case-control study on asphalt workers and lung cancer.

In 2005 he was granted an EU-EPITOK grant to work for four months at the NOFER institute in Lodz in Poland.

In 2006 he obtained a postdoctoral fellowship within the European Union ECNIS programme at the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO).

LIST OF PUBLICATIONS

INTERNATIONAL JOURNALS

De Vocht F, Stevens T, Glover P, Sunderland A, Gowland P, Kromhout H. Cognitive Effects of Exposure to Stray Fields Generated by a 7 Tesla Ultra-High Field MRI Magnet. *NeuroImage; provisionally accepted.*

De Vocht F, Huizer D, Prause M, Jakobsson K, Peplonska B, Straif K, Kromhout H. Field comparison of inhalable aerosol samplers applied in the european rubber manufacturing industry. Int Arch Occup Environ Health 2006; 79(5):.

De Vocht F, Stevens T, van Wendel-de-Joode B, Engels H, Kromhout H. Acute neurobehavioral effects of exposure to static magnetic fields: Analyses of exposure-response relations. J Magn Reson Imaging 2006; 23(3): 291-297.

De Vocht F, van Drooge H, Engels H, Kromhout H. Exposure, health complaints and cognitive performance among employees of an MRI scanners manufacturing department. J Magn Reson Imaging 2006; 23(2): 197-204.

De Vocht F, Straif K, Szeszenia-Dabrowska N, Hagmar L, Sorahan T, Burstyn I, Vermeulen R, Kromhout H. A database of exposures in the rubber manufacturing industry: design and quality control. Ann Occup Hyg 2005; 49(8): 691-701.

De Vocht F, Zock JP, Kromhout H, Sunyer J, Anto JM, Burney P, Kogevinas M. Comparison of self-reported occupational exposures with a job exposure matrix in an international community-based study on asthma. Am J Ind Med 2005; 47(5): 424-442.

Chakeres DW, de Vocht F. Static magnetic field effects on human subjects related to magnetic resonance imaging systems. Prog Biophys Mol Biol 2005; 87(2-3): 255-265.

De Vocht F, van-Wendel-de-Joode B, Engels H, Kromhout H. Neurobehavioral effects among subjects exposed to high static and gradient magnetic fields from a 1.5 Tesla magnetic resonance imaging system—a case-crossover pilot study. Magn Reson Med. 2003; (50(4): 670-674.

NATIONAL JOURNALS

F. de Vocht. Book review. Exposure assessment in occupational and environmental epidemiology. Tijdschrift voor toegepaste Arbowetenschap (Journal of Applied Occupational Sciences). 2004; 2: 22-23.

REPORTS

EU-EXASRUB consortium. Final Report – Improved Exposure Assessment for Prospective Cohort Studies and Exposure Control in the Rubber Manufacturing Industry(QLK4-CT-2001-00160 and QLK4-CT-2002-02786 (NAS extension). European Commission Quality of Life and Management of Living Resources Programme, Fifth Framework Programme, Key Action 4.

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