The Magnetized brain

Lotte van Nierop
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The Magnetized brain

Working mechanisms for the effects of MRI-related magnetic fields on cognition, postural stability, and oculomotor function

De gemagnetiseerde hersenen
Werkingsmechanismen voor de effecten van MRI-gerelateerde magneetvelden op cognitieve-, balans- en oculomotor functies

(met een samenvatting in het Nederlands)

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Chapter 1

Introduction

1.1 BACKGROUND OF MAGNETISM

More than 1000 years B.C. a shepherd noted that the iron nails in his sandals were drawn to the ground while walking on Mount Ida, Turkey. He dug into the earth and discovered that some stones (magnetite) harbored attractive forces (Mourino 1991). With this very first discovery of a magnet, magnetism and magnetic forces, the search for answers to understand and explain this phenomenon was initiated. Scientific research led to the understanding of physical characteristics of magnetism described in different laws, theories and mathematical equations. Nowadays magnets and magnetism are applied in many products like a compass, dynamo, 'magnetic memory' and an MRI scanner.

1.2 HISTORY AND TRENDS IN MRI

The basis for magnetic resonance imaging (MRI) was laid in 1924 by Gerlach and Stern who demonstrated that the magnetic moment of a silver atom is deflected by a molecular beam when placed in an inhomogeneous magnetic field (Geva 2006). In 1977 the development of this principle enabled new imaging techniques of the human body (Damadian et al. 1977). The invention and application of MRI resulted in three Nobel prizes which were awarded in 1944 (Isidor Rabi), 1952 (Bloch and Purcell) and 2003 (Lauterbur and Mansfield). MRI is now an important imaging technique in addition to X-ray and CT scans, with more than 205 systems in use in the Netherlands (Schaap et al. 2013). Over the years, the field strengths of the MRI magnets increased from the earliest 0.04 Tesla (T) scanner (Edelstein et al. 1981) to the recent ultra-high field scanners of 14 T (Duyn 2012). The higher field strengths improved the quality of the image (see Figures 1 and 2) and introduced new applications like functional MRI (fMRI). Another trend is the use of MRI during medical and clinical intervention procedures (Gowland 2005; Hall et al. 2000).

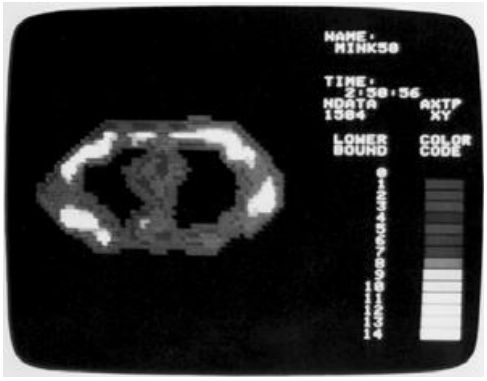

Figure 1 First human MRI scan in 1977 at 0.05 T of the abdomen, took 5 hours (Damadian et al. 1977)

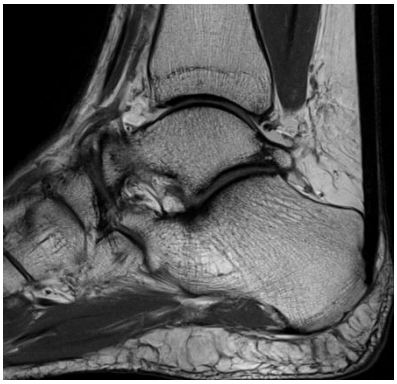

Figure 2 MRI scan in 2009 at 1.5 T of the ankle, took about 20 minutes (SiemensHealthCare 2009)

1.3 MAGNETIC FIELDS RELATED TO MRI

To create an MRI image, three types of electromagnetic fields are used: a static magnetic field, a gradient magnetic field and a radiofrequency magnetic field; see Figure 3. The static magnetic field (SMF) is used to line up all hydrogen atoms in the body in one spatial direction. During a scanning procedure a pulsed time gradient and radiofrequency magnetic fields are also present. The pulsed gradient fields spatially encode the position of the protons by varying the magnetic field linearly across the imaging volume. The energy of the radio pulse is absorbed by the hydrogen proton in the nuclei, which thereby gains energy (excitation). This energy is re-emitted by the nucleus (relaxate) and detected by a receiver coil after the radio pulse stops. The energy detected by the coils can be translated into a picture. The exposure to pulsed gradient and radiofrequency fields is not further discussed in this thesis.

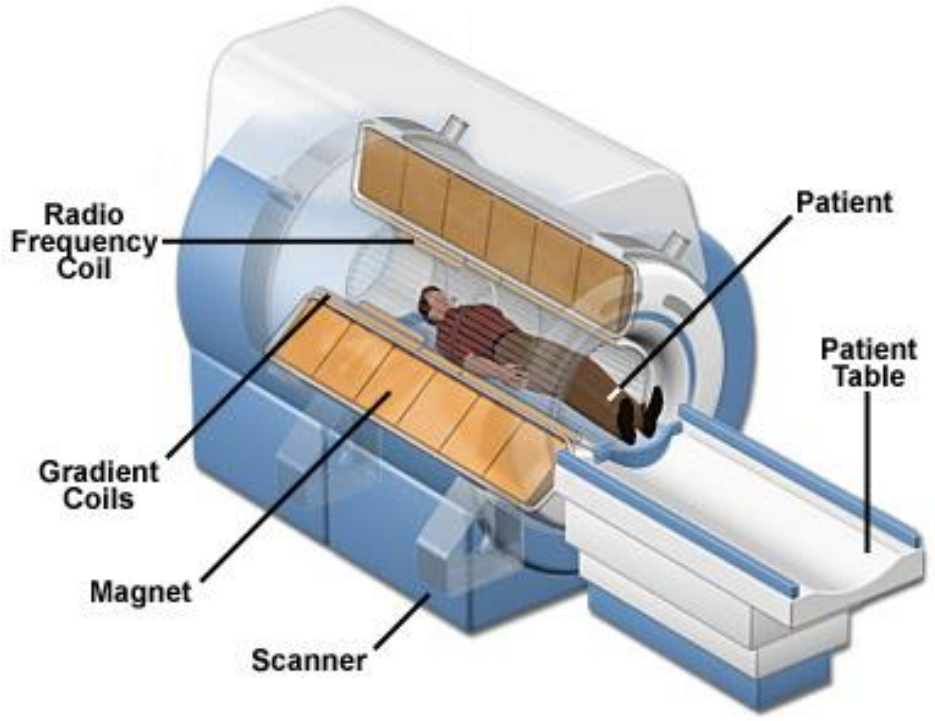

Figure 3 An MRI scanner cutaway with the position of the magnet, gradient coils and radiofrequency coils visible in the scanner bore around the subject (Coyne 2014).

1.4 EXPOSURE TO MRI-RELATED (STRAY) STATIC MAGNETIC FIELDS

The SMF in the bore of the MRI is homogeneous in the x, y and z directions. At the end of the bore, the strength of the magnetic field decays with distance and results in an inhomogeneous gradient, the 'stray static magnetic field'. The shape and course of the stray fields depend on the strength of the scanner and the protection of the magnet by active shielding coils. These (stray) SMFs are also present when no scanning procedure is taking place (stand-by modus) because high-field MRI systems are never ramped down due to the very time demanding and expensive procedure to bring the machine on field. Consequently, employees working with MRI are repeatedly exposed to stray magnetic fields around the MRI scanner, e.g. radiographers, radiologists, surgeons, anesthesiologists and cleaning staff, but also physicists and engineers in constructing, maintaining and testing of MRI scanners

(Gowland 2005). Beside exposure to the stray SMF, an additional exposure is generated by moving in the (stray) fields of the MRI-scanner, resulting in a low-frequency movement-induced time-varying magnetic field (TVMF). The intensity of the TVMF depends on the strength of the gradient field and the speed of movement.

With the increased use of MRI, scanning with higher field strengths, and use of novel (interventional) procedures, concerns about possible adverse health and behavioral effects have been raised. Especially for employees who are exposed on a daily basis to the stray SMF and movement-induced TVMFs. Therefore, the studies described in this thesis focus on the effects of exposure as experienced by employees in the stray SMF of the MRI scanner, and not on patients exposed to a homogeneous SMF who are additionally exposed to pulsed time gradient and radiofrequency magnetic fields.

1.5 HAZARDS RELATED TO (STRAY) STATIC MAGNETIC FIELDS

The most important safety hazard in the MRI room is the presence of ferromagnetic objects which can become dangerous projectiles when attracted by the magnet (Colletti 2004; Scarabino et al. 2003). Furthermore, sensory symptoms are reported by employees when in the vicinity of the scanner, such as nausea, dizziness, vertigo, metallic taste, headache, and fatigue (Atkinson et al. 2007; de Vocht et al. 2006b; Feychting 2005; Glover et al. 2007; Heilmaier et al. 2011; Heinrich et al. 2013; Patel et al. 2008; Schaap et al. 2014; Schenck 1992; Schenck et al. 1992; Wilen et al. 2011). These symptoms become more prevalent with increasing field strengths and duration of exposure (Chakeres et al. 2005; de Vocht et al. 2006b).

Exposure to the stray SMF is known to induce several sensory changes. It is therefore of primary importance to investigate whether behavioral functions might also be affected by (stray) SMF exposure. For some of the reported symptoms, e.g. nausea, dizziness, and vertigo, a mediating role for the vestibular system has been suggested (Glover et al. 2007). Therefore, the first objective of this thesis is to explore whether cognitive and vestibular related functions are affected in the stray SMF of an MRI scanner.

Cognition

The broad range of functions cooperating to carry out, understand and consciously experience any task or action in daily life is referred to as cognition and involves mechanisms of how we perceive, process, store and express information. Although cognitive functions are conceptually distinguishable, they are inextricably bound together, integrated within tasks and behavioral measures. Assessment of cognitive or neuropsychological tests gives a behavioral indication of the underlying (mal)function of neuronal mechanisms and biological processes (Lezak MD 2004).

Within earlier experimental research, healthy volunteers exposed to a 1.0 T SMF in front of the scanner showed a decreased eye-hand coordination and visual contrast sensitivity (de Vocht et al. 2007b; de Vocht et al. 2003). Studies where additional body or head movements were performed within the stray fields revealed reduced voluntary visual tracking performance and speed of eye-hand coordination (de Vocht et al. 2007b; de Vocht et al. 2006a) (see Table 1 for an overview of earlier performed studies). It is unknown whether these behavioral changes could be attributed to the stray SMF or to the movement-induced TVMF, and how long-lasting these effects are. However, it has been suggested that the effects are transient and disappear rapidly after exposure (de Vocht et al. 2006b).

The vestibular system

The vestibular system is better known as the balance system. It senses absolute head orientation relative to gravity and head accelerations. The vestibular system enables perception of head motion and orientation, controls eye movements to stabilize visual images on the retina (vestibulo-ocular reflex), and controls body posture to maintain balance in stance and during locomotion (vestibule-spinal reflex). Moreover, the vestibular system is involved in cognitive functions like spatial orientation (Angelaki et al. 2008). Direct and indirect methods to define performance of the vestibular system are done by measuring e.g. the vestibulo-ocular reflex, postural stability, and oculomotor functions upon stimulation (Lang et al. 2010).

The vestibular system consists of a labyrinth which is located in each inner ear, from here vestibular nerves connect via the brainstem and cerebellum to several cortical areas. Visual and proprioceptive information is continuously integrated throughout the central vestibular pathway, making it a convergent and strongly multimodal pathway (Desmond 2011).

The labyrinth structure itself has several sensors to detect changes in head position:

- Three semicircular canals that are at right angles to each other, detect angular accelerations. Sensory hair cells detect the movement of the endolymph fluid in the canals, as they are embedded in a small membrane (the cupula) that is surrounded by and moves with the endolymph.
- The otolith organs (utricle and saccule) detect head tilt relative to gravity, as well as head translation and rotation: a layer of sensory hair cells detect the relative displacement of the heavy and dense calcium carbonate crystals on top of it.

In previous studies, exposure to MRI-related SMFs revealed behavioral changes in rats of decreased rearing (Houpt et al. 2005), circling behavior (Houpt et al. 2003; Houpt et al. 2005), and conditioned taste aversion (Houpt et al. 2003; Houpt et al. 2005; Nolte et al. 1998). These behavioral changes were hypothesized to have a vestibular component which was later confirmed by labyrinthectomized rats who did not show the above described behavioral responses (Cason et al. 2009), and freely entered a 2 T field, in contrast to normal rats who refused to enter (Houpt et al. 2007).

These experimental studies provided the first indication that potentially also among humans an effect from exposure to (stray) static magnetic fields on several behavioral and vestibular related functions could be expected. Yet, whether the SMF, movement-induced TVMF, or the combination of both results in a change of behavioral functions needs further investigation. Therefore, as a second objective in this thesis, we try to disentangle the behavioral changes as raised by the stray SMF alone versus in combination with movement-induced TVMF exposure.

Table 1 Summary of previous experimental research on cognitive-based changes due to MRI-related (stray) static magnetic fields.

Authors, Date	Field	Field strength	Affected functions [a]	Not-affected functions
Chakeres et al. 2003	SMF	0.05 and 8.0 T	Recognition of verbal memory	-Learning and retention -Verbal fluency -Verbal attention -Verbal working memory
de Vocht et al. 2003	stray SMF+ TVMF	1.5 T	Precision of pursuit aiming	-Visuomotor coordination -Verbal and visual memory -Visual acuity
de Vocht et al. 2006a	stray SMF+ TVMF	0; 1.5 and 3.0 T	-Speed of pursuit aiming -Speed of visual tracking -Recall of visual and auditive memory	-Visual scanning -Visual acuity
de Vocht et al. 2007b	stray SMF+ TVMF	0; 0.8; 1.6 T	-Speed of visual tracking	-Visuomotor coordination -Verbal working memory -Visual acuity

[a] All functions were negatively affected at $p<0.05$ by exposure

1.6 ASSESSED TESTS

Internationally registered tests were chosen and pilot tested based on the following criteria: availability of parallel versions, sensitive to pick up acute (temporal) changes, free of education level of subject, free of practice and ceiling effects, and compatible with MRI environment (see Table 2).

Within the three experimental studies described in this thesis we used a test battery, including tests which showed an effect of exposure in previous research (de Vocht et al. 2007a; de Vocht et al. 2007b; de Vocht et al. 2006a; de Vocht et al. 2003). In addition, other tasks were selected for cognitive domains that are relevant for surgeons and other medical professionals operating near MRI systems, for example, visuoperception and spatial orientation as well as more general functions concerning attention, concentration, and (working) memory. Furthermore, domains related to the reported sensory symptoms of nausea and dizziness were included, such as spatial orientation (Oman 1982) and haptic perception.

Vestibular tests evaluating postural stability, oculomotor function and nystagmus were included. The most commonly used tests were selected and adapted for use in an MRI environment. The vestibulo-ocular reflex at different frequencies was assessed outside of the MRI environment.

Table 2 Cognitive, postural stability and oculomotor tasks assessed in the three conducted experiments described in this thesis.

Domain	Test	Description	Variable	Experiment 1	2	3
Memory	Long term memory story recall(RBMT)	Recall of a short story read by the test leader	Amount of correct words	■	■	■
	Long term memory picture recall (MCG)	Recall of a picture as shown by the test leader	Amount of correct drawn line	■	□	■
	Letter-number sequencing task (WAISIII)	Reproduce and order letters and numbers in logical order	Length of last repeated sequence multiplied by amount of correct recalled rows	■	□	■
Attention	Symbol cancellation task	Cancel one target symbol out of different symbols in 60 seconds	Speed as correct cancelled items	■	□	■
	Reaction time task; simple, complex, and inhibition level	Press the target button when alights and return to the home button with different levels; Simple task; one button option Complex task; 9 button options Inhibition task; press button left from alighting button	Reaction time; time to release home button after alight of target button Motion time; time to go from home to target button Disengagement time; time needed to release target button	■	■	■
Spatial-orientation	Roadmap task	Left right orientation on a city map	Time to complete task	■	□	■
	Judgment of Line Orientation task (JULO)	Judge the orientation of 2 tilted lines with reference lines	Correct judged lines	■	□	■
	Line bisection task	Mark the middle of 20 horizontal lines	Deviation as percentage from center of the line (100)	■	■	■
Haptic perception	Kappers task	Haptically blindfold place a bar in parallel position with a reference bar	Absolute deviation in degrees	■	□	■
Visual perception	Visual tracking task	Track of 9 entangled lines	Tracking speed	■	□	■
	Contrast sensitivity (F.A.C.T.)	Recognize the direction of lines with shrinking contrast and different cycle frequencies	Contrast sensitivity level in cycles per degree	■	■	■
Visuomotor coordination	Pursuit Aiming task	Place dots within small circles in 60 seconds	Speed as total items Precision as % correct response of total	■	■	■
Postural stability	Romberg task; feet parallel or in tandem	Stand barefoot with arms alongside the body and eyes closed	Sway path, area, and velocity Sway path, area, and velocity	■	■	■
Oculomotor functions	Smooth pursuit	Fixate and track of a sinusoidal stimulus	Gain and phase	□	■	■
	Saccades	Fixate and track of a stimulus to the right, middle, and left	Velocity, accuracy, and latency	□	■	■
Vestibular-ocular reflex	Nystagmus	Spontaneous eye movements by fixate to an imaginary point in darkness with eyes closed	Slow phase eye movement	□	■	■
	Caloric reflex test	Spontaneous eye movements by fixate to an imaginary point in darkness with eyes closed	Slow phase eye movement and unilateral weakness	□	■	□
	Rotary chair test	Spontaneous eye movements by fixate to an imaginary point in darkness with eyes closed	Slow phase eye movement	□	■	□

1.7 PROPOSED WORKING MECHANISMS

The previously reported sensory symptoms as raised in the magnetic fields have been attributed to several potential mechanisms working via the vestibular system (Glover et al. 2007; Schenck 2005; Schenck et al. 1992). The behavioral changes related to cognition have been attributed to the field gradient and motion within a SMF (Chakeres et al. 2005; de Vocht et al. 2006a; de Vocht et al. 2003). However, neither an elaborated working mechanism nor a theoretical (and practical) paradigm about the translational mechanisms for the (specific) behavioral outcomes has been proposed. The last objective of this thesis is therefore to find evidence for (a) working mechanism(s) underlying the behavioral changes when exposed to the MRI-related magnetic fields.

It is known that magnetic fields can interact with elements in the body that possess magnetic properties. At the cellular level, a magnetic field can change chemical reactions by e.g. magnetoresistance, magnetostriction or magnetic torques. These generated forces and mechanisms, however, only play a role at field strengths of at least 10 Tesla or higher (Formica et al. 2004; Schenck 1992; Schenck 2005). Within a human body other mechanisms can become important when present in a magnetic field, e.g. magnetic susceptibility of tissues, magnetohydrodynamic forces (MHD), Lorentz forces (as part of the MHD) and electromagnetic induction (Miranda 2005).

Magnetohydrodynamic forces result from the interaction between a static magnetic field and a conducting moving fluid. For example, moving body fluid is generated by motion of the body itself or internal motion of a body fluid (e.g. blood). The induced current in the fluid generates forces and can also change the magnetic field itself. This only becomes meaningful when moving in magnetic fields above 10 T (Schenck 1992; Schenck 2005).

Lorentz forces result from the interaction between a static magnetic field and a moving object. The magnitude of these forces is dependent on the speed of the moving object, and these forces curve the object perpendicular to the direction of the magnetic field force and the instantaneous velocity of the object.
Besides the magnetic component of the Lorentz force there is also an electrical force which can accelerate or decelerate the moving object in the same linear orientation as the electrical field. It is suggested that these Lorentz forces are raised within the

endolymph fluid of the semicircular organs of the vestibular system upon exposure to a 3.0 T SMF (Roberts et al. 2011).

Electromagnetic induction is caused by a changing flux density of magnetic field lines which induces a flow of electric current in a conductor (better known as Faradays Law); meaning that moving through a magnetic field (resulting in a change in magnetic flux) induces an electrical current in the body. This is particularly important in parts of the body that communicate via electrical signals, like neurons in the nervous system and the brain. These signaling pathways of neurotransmission can be disturbed (inhibition or excitation) by interference of external electrical pulses.

Especially the Lorentz forces and Electromagnetic induction seem plausible theories for inducing vestibular and cognitive changes, respectively, upon magnetic field stimulation. However, no elaborated working mechanism regarding specific behavioral outcomes has been described so far. Within the general discussion of this thesis all possible working mechanisms underlying identified cognitive and vestibular changes will be discussed and further explained.

1.8 AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on identifying the effects of exposure to the stray SMF and TVMF on behavioral functions of cognition, postural stability, oculomotor functions, and on unraveling an underlying mechanism. The three main objectives are:

- Explore behavioral domains and functions affected by exposure to a SMF and TVMF
- Disentangle the behavioral changes induced by SMF and TVMF exposure
- Identify working mechanisms underlying the behavioral changes

To this end we performed three experimental studies. In the **first experiment,** healthy subjects were exposed to the stray SMF of a 7 T MRI with additional head movements inducing a TVMF. A broad range of earlier and newly identified cognitive functions (Chapter 2), postural stability and oculomotor performances were assessed (Chapter 5). The presence of an exposure-response relationship was

investigated for these tasks. In addition, in this study the use of quantitative personal exposure measurements in experimental research was evaluated (Chapter 3).

In a **second experiment** the effects of exposure to only SMFs or to the combination of SMFs and TVMFs on cognitive functions (Chapter 4), postural stability, and oculomotor performance (Chapter 6) were disentangled. In addition, test performances within the magnetic fields were studied among subjects with low versus high vestibular responsiveness (Chapter 7) in order to gain insight into a potential mediating role of the vestibular system.

The role of the vestibular system in magnetic field induced behavioral changes was further studied in a **third experiment.** Here, cognitive, postural, and oculomotor performances upon exposure to MRI-related magnetic fields were compared with performances after direct stimulation of the vestibular afferents by Galvanic Vestibular Stimulation (Chapter 8).

The main findings of the studies and possible underlying working mechanisms are discussed and placed into a broader context in a general discussion (Chapter 9).

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Chapter 2

Effects of magnetic stray fields from a 7 Tesla MRI scanner on neurocognition: a double-blind randomized crossover study

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ABSTRACT

This study characterizes neurocognitive domains that are affected by movement-induced Time-varying Magnetic Fields (TVMF) within a Static Magnetic stray Field (SMF) of a 7 Tesla (T) Magnetic Resonance Imaging (MRI) scanner. Using a double blind randomized crossover design, 31 healthy volunteers were tested in a sham (0 T), low (0.5 T) and high (1.0 T) SMF exposure condition. Standardized head movements were made before every neurocognitive task to induce TVMF. Of the six tested neurocognitive domains, we demonstrated that attention and concentration were negatively affected when exposed to TVMF within an SMF (varying from 5.0% to 21.1% per Tesla exposure, $p<0.05$), particular in situations were high working memory performance was required. In addition, visuospatial orientation was affected after exposure (46.7% per Tesla exposure, $p=0.05$). Neurocognitive functioning is modulated when exposed to movement-induced TVMF within an SMF of a 7 T MRI scanner. Domains that were affected include attention and concentration and visuospatial orientation. Further studies are needed to better understand the mechanisms and possible practical safety and health implications of these acute neurocognitive effects.

2.1 INTRODUCTION

The use of MRI scanners as a diagnostic instrument or to guide interventions increased rapidly since its introduction in the late 1970s, and this trend is expected to continue (Gowland 2005). For example, the amount of scans produced each year in hospitals throughout the Netherlands increased from 227,000 in 1998 to around 682,000 in 2008 (Schaap et al. 2013). Simultaneously, the applied intensity of the magnetic field increased from 0.04 Tesla (T) in the 1980s to 7 T and 11.7 T of the recently available ultra-high field scanner systems (Edelstein et al. 1980; Hu et al. 2004; Theysohn et al. 2008). Nowadays, 3.0 T scanners are replacing 1.5 T scanners for intervention and routine clinical applications, while scanners of >7 T have started to appear in academic settings.

Scanning with higher field strengths improves imaging quality, reduces imaging time and increases the image quality of dynamic systems such as the circulatory system (Gowland 2005). To create an MRI image, three types of electromagnetic fields are required: a static magnetic, switched gradient magnetic field and a radiofrequency electromagnetic field. Of these, the static magnetic field (SMF) is always present, even when no actual imaging procedure is taking place. This is because most MRI systems are never ramped down since inoculation of the machine is very time demanding and expensive. The magnetic fields inside the magnet bore are completely homogenous; this in contrast to the spatially very heterogeneous fields surrounding the magnet bore that are often referred to as SMF. When individuals move through these heterogeneous stray fields, a change in gradient is brought about that induces a time-varying magnetic field (TVMF).

The introduction of stronger MRI systems has resulted in increased exposure to SMF for both patients and personnel in healthcare, research and industry. To date, mainly safety and health concerns for patients have been evaluated, but possible consequences are particularly important for professionals including radiographers, radiologists, anesthesiologists, nurses, cleaners and MRI engineers since they are repeatedly exposed to SMF and TVMF while working with or in the neighborhood of MRI scanners. Employees moving in the stray fields surrounding these systems have reported symptoms like nausea, dizziness, fatigue, sleeplessness, concentration problems and a metallic taste (Chakeres et al. 2003b; de Vocht et al. 2006b; Schenck 1992; Schenck et al. 1992; Wilen et al. 2011). Beside such symptoms, even subtle temporary effects of exposure to electromagnetic fields

might affect their behavior and cognitive performance, which consequently could have implications for their own safety and that of their patients. Especially, the work of surgeons and personnel performing MRI guided interventions and operations requires a high level of precision and performance (Hall et al. 2001; Henk et al. 2005; Liu et al. 2000; Martin et al. 2000; Razavi et al. 2003).

Previous experimental studies with volunteers found no neurocognitive effects from neither homogeneous SMF inside the magnet bore (Chakeres et al. 2003a; Schenck 2000; Schenck et al. 1992) nor from TVMF alone (de Vocht et al. 2007a). However, movement-induced TVMF in a SMF near a 1.5, 3.0 and 7 T MRI scanner was shown to have small but statistically significant reversible acute neurobehavioral effects on visual perception and visuomotor performance (de Vocht et al. 2007b; de Vocht et al. 2006a; de Vocht et al. 2003). In one of these, studies working memory was affected as well (de Vocht et al. 2006a). It has been hypothesized that these effects probably arise due to induced electrical currents in the body that are generated during movement in a SMF (de Vocht et al. 2007b; Glover et al. 2007).

Given the above, there is an urgent need for more research on acute effects of movement-induced TVMF near MRI scanners. The aim of the present study was to characterize potential acute neurocognitive effects of exposure to TVMF within a SMF in a double-blind randomized crossover trial. For this purpose, a test battery has been composed that is sensitive to acute (temporal) changes in susceptible neurocognitive domains that are relevant for surgeons and other personnel in a working situation near MRI systems. In addition, domains were included that are associated to the reported symptoms of nausea and dizziness near MRI systems and domains that showed effects in earlier studies.

2.2 METHODS

Subjects

Thirty-one healthy volunteers who signed an informed consent participated in the experiment. Most were students (N=24) from Utrecht University, recruited by flyers and advertisement on bulletin boards. Thirty subjects finished at least pre-university education, and one subject finished higher general secondary education. Of all volunteers, 10 were men and 21 were women with an average age of 23.8 (SD 6.4) years. Applied exclusion criteria were self-reported presence of MRI-incompatible elements in the body, history of neurological disease, serious vision deficiencies, use of medication (except for birth control), soft or hard drugs, excessive alcohol (>2 glasses per day) or coffee (>5 cups per day) and sensitivity to motion sickness in adulthood. Sensitivity to motion sickness was defined as a score higher than two on a four-point Likert scale ranging from one (not at all) to four (very often) for at least one of three types of symptoms. Eight subjects reported to have undergone an MRI but none of the subjects or experimenters had worked with MRI or had seen the test room before. A modest incentive gift voucher was given as expenses for every completed test session. The study was approved by the local medical ethics committee of the University Medical Center Utrecht (UMCU), the Netherlands.

Experimental design

A double-blind randomized crossover design was used in which each subject was tested for 1 hour on three occasions, conducted at the same time of day with 1 week between each session (see figure 1).

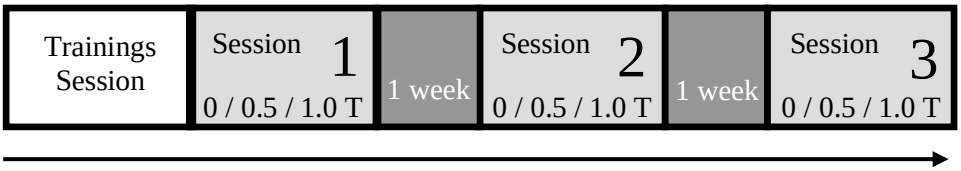

Figure 1 Setup of the experiment. Each subject underwent three test sessions with one week in between at the same time of the day. Exposure conditions were randomized over the subjects. The first session was preceded by a training session.

The sequences of exposure were balanced and assigned to each subject prior to the start of the experiment using a randomization protocol. There were two active exposure conditions of 0.5 T (low) and 1.0 T (high) SMF (in the stray field of a passively shielded 7.0 T Philips Achieva research system located at University Medical Center Utrecht) and an unexposed sham condition (<25 mT) in a separate room (see figure 2). The subject sat on a fixed chair, with their back towards the bore at, respectively, 47 and 86 cm for the 1.0 and 0.5 T condition. In addition to the SMF in the exposure conditions, subjects were exposed to TVMF induced by standardized head movements before each new neurobehavioral test in the test battery (see table 1). The head movements consisted of 10 movements in vertical and 10 in horizontal direction (covering an angle of 180 degrees in 0.8 s), the start of each movement indicated by an auditory cue. The accompanying TVMF at head height in sitting position in the 0.5 (low) and 1.0 T (high) conditions were on average approximately 1200 and 2400 mT/s, respectively, as measured by a static magnetic field dosimeter (Magnetic Field Dosimeter; University of Queensland, Australia, (Fuentes et al. 2008). Several measures were taken to ensure a double-blind experiment: subjects were tested inside a standardized tent (210x140x190 cm) to hide the exposure condition. In addition, in the sham condition, an audiotape playing the acoustic noise of an MRI system was used. The subject and trained experimenter were blind guided into one of the tents by the experiment coordinator (LvN). To reduce a possible practice effect in neurocognitive test performance, the subjects completed a full test session prior to the first experimental session. Before each session, subjects were checked for metallic components and were asked to complete a questionnaire about current symptoms. A second questionnaire on (adverse) side effects and perception of the actual exposure condition was completed after each session.

Table 1 Design of a single test session. During approximately 50 minutes 12 different cognitive tasks were performed each preceded by standardized head movements (Smiley☺), ten movements in vertical and ten movements in horizontal direction.

Time		Task	Short description of task
1'	1a	RBMT Long term memory task	Recall of a short story read by the test leader
		☺	
	2a	MCG Long term memory task	Recall of a picture shown by the test leader
		☺	
	3a	Letter-number sequence	Recall of a random letter-number series in order of the alphabet and number system
		☺	
	4	Roadmap task	Follow a route on a map with a pencil and point out to turn left or right as fast as possible
		☺	
	5	Kappers task	Turn a bar (blinded) with the left/ right hand in parallel position with a reference bar at the other hand
		☺	
	6	Line bisection task	Mark the middle of 20 horizontal lines as fast as possible
		☺	
	7	Visual tracking task	Track with a pencil multiple tangled lines on paper as fast as possible
		☺	
	8	Judgment of Line Orientation task	Judge the orientation of 30 different lines with a corresponding example as fast as possible
		☺	
	9	Cancellation task	Scan lists of symbols and cancel out one specific symbol in 60 seconds
		☺	
	10	Pursuit aiming task	Place dots in small circles in 60 seconds
		☺	
	11	F.A.C.T.	Recognize the direction of lines with shrinking contrast with one blinded eye
		☺	
	3b	Letter-number sequence (repeated)	Recall of a random letter-number series in order of the alphabet and number system
		☺	
	1b	RBMT (recall)	Recall the short story read by the test leader at the start of the session
		☺	
	2b	MCG (recall)	Recall the picture shown by the test leader at the start of the session
		☺	
	12.1	Reaction time task (simple)	Press the target button when it alights and return to the home button (1 option), 30 repeats
		☺	
	12.2	Reaction time task (complex)	Press the target button when it alights and return to the home button (9 options), 30 repeats
		☺	
50'	12.3	Reaction time task (inhibition)	Press the target button left to the one that alights and return to the home button (8 options), 30 repeats

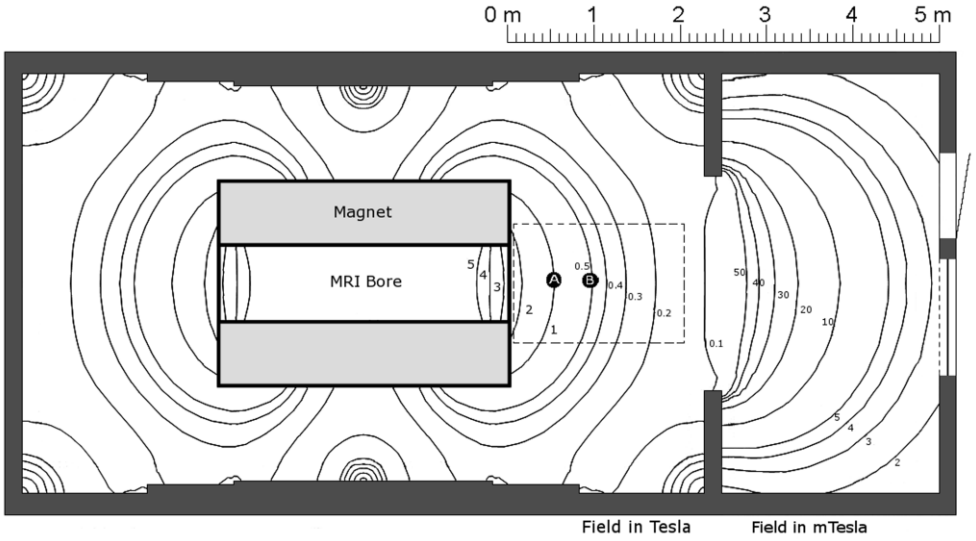

Figure 2 Top view map of the 7 T MRI with calculated field lines of the SMF as provided by Magnex Scientific Inc. Dots represent the positions of the subject for the exposure conditions within the tent. Position A represents the 1.0 T condition and position B the 0.5 T condition, respectively 47 and 86 cm in front of the bore. The tent (interrupted line) was shifted when subject was in position B. The control condition was in a room opposite to the scanner room.

Test battery

Neurocognitive domains were selected based on brain functions that are most relevant for surgeons and other medical professionals operating near MRI, for example, visual perception, motor performance as well as more general functions concerning attention, concentration and (working) memory (see table 1 and supplementary material). In addition, domains related to the reported sensory symptoms of nausea and dizziness were included like spatial orientation (Oman 1982) and haptic perception.

Based on the results of a pilot test (data not shown), the test battery was composed of tasks that are relatively short (<4 min each), insensitive to ceiling effects and to influences of practice and level of intelligence. This was because the change in performance is expected to be subtle, acute and short-lived in educated and healthy individuals. For this reason, we also included the time needed to complete a task in addition to task performance per se. Above all, the test battery had to be compatible and safe for use in an MRI environment and for the different sessions, parallel versions of all tests were used.

Based on the results of previous studies (de Vocht et al. 2007b; de Vocht et al. 2003; de Vocht et al. 2006b), tests selected for visual perception were the visual tracking task (World Health 1986) and a visual acuity task (F.A.C.T.®). For integration of visual and motor performance the pursuit aiming task (World Health 1986) was included. To assess attention and concentration we selected two tasks; the symbol cancellation task (Diller, Ben Yishay et al., 1974 in (Lezak et al. 2004)) and a reaction time task with a simple-, complex- and inhibition section (van Zomeren et al. 1987; van Zomeren et al. 1984). Beside reaction time, this task also measures visuomotor performance, motion time and disengagement time by registration of initiation-, release-, movement- and return times of the home- and target button. To measure the performance of memory (episodic learning) we used the Rivermead Behavioral Memory Test (RBMT) story recall for verbal memory (Wilson, Cockburn and Baddeley, 1989 in (Lezak et al. 2004)) and Medical College of Georgia (MCG) figure for nonverbal memory (Loring and Meador, 2003 in (Lezak et al. 2004)). For working memory, the short version of the WAIS III letter-number sequencing test (Wechsler, 1997 in (Lezak et al. 2004)) was administered twice throughout the test session by two different versions to check for a possible decrease in attention or motivation. To assess nausea and dizziness-related functions, tests for visuospatial orientation were specified into different aspects of spatial orientation by the judgment of line orientation task for angular relation (Benton et al. 1994), the roadmap task for left-right orientation (Money, 1976 in (Lezak et al. 2004)) and the line bisection task for spatial representation (Schenkenberg et al., 1980 (Lezak et al. 2004)). To explore the tactile modality, haptic perception was tested by use of the Kappers task (Kappers et al. 1999). (For a more detailed description of the tasks see table 1 and supplemental table S1).

Data analysis

Statistical analyses of inter-individual and intra-individual differences in test performance in association with exposure were performed using mixed-effects models (Laird et al. 1982) in SPSS V.16.0 (SPSS Inc.). The exposure conditions (0, 0.5 and 1.0 T) were entered as continuous exposure variable assuming linear exposure-effect associations. All analyses were adjusted for session number, gender and reported 'ever experienced mild symptoms of motion sickness (see paragraph 'subjects'). Random effects were modelled using heterogeneous compound symmetry

that assumes similar correlation between residuals of the same subject but no correlation between different subjects.

The data and residuals from the visual tracking task, roadmap and judgement of line orientation were log10 transformed to account for potential ceiling effects. F.A.C.T. data were also log10 transformed since the relationship between the steps is not linear (Gilmore 2002), and the data of the RBMT story recall were converted into percentages to obtain a better normalized distribution. Statistical significance level was defined as $p \leq 0.05$.

2.3 RESULTS

Of the 31 eligible subjects, one subject decided to withdraw from the study due to non-experimental-related reasons. In total, 30 subjects completed all three experimental sessions. An experimental session had an average duration of 51 (SD 6) min for each participant conducted at the same time of day ±52 (SD 48) min. The mean test scores and SDs for all tests in the three different exposure conditions are presented in table 2.

Table 3 shows results of the main analyses using a continuous exposure model. With respect to the visual-motor domain and the interaction between the visual and motor domain as measured by the visual tracking task, F.A.C.T. and pursuit aiming task, no statistically significant effects of exposure were observed.

However, more general functions like attention and concentration, assessed by the reaction time task, showed a significant exposure-response association on motion time in the inhibition reaction time task (+5.0% per Tesla exposure $p<0.05$) reflected in increased times to move to the target button at higher exposure levels. In addition, disengagement time was negatively affected in the simple reaction time task (+21.1% per Tesla exposure $p<0.001$), complex reaction time task (+9.6% per Tesla exposure $p<0.01$) and inhibition reaction time task (+8.9% per Tesla exposure $p<0.01$), see figure 3. As such, increased exposure resulted in a longer time to release the target button in order to return to the starting position. The symbol cancellation task did not show a significant difference between the exposure conditions nor did the WAISS letter-number sequencing task testing working memory itself.

Episodic learning for verbal and nonverbal memory was not affected in the Rivermead Behavioural Memory Test story recall (RBMT) and Medial College of Georgia figure (MCG). However, the RBMT reached borderline statistical significance (p=0.07).

Domains that are related to nausea and dizziness, such as spatial orientation, showed an exposure-response association at the line bisection task indicating that the percentage deviation from the true middle of the line raised (+46.7% per Tesla exposure p=0.05) with increased exposure. The judgement of line orientation and roadmap task did not reveal an effect of exposure nor did the Kappers task demonstrate an effect of exposure on haptic perception.

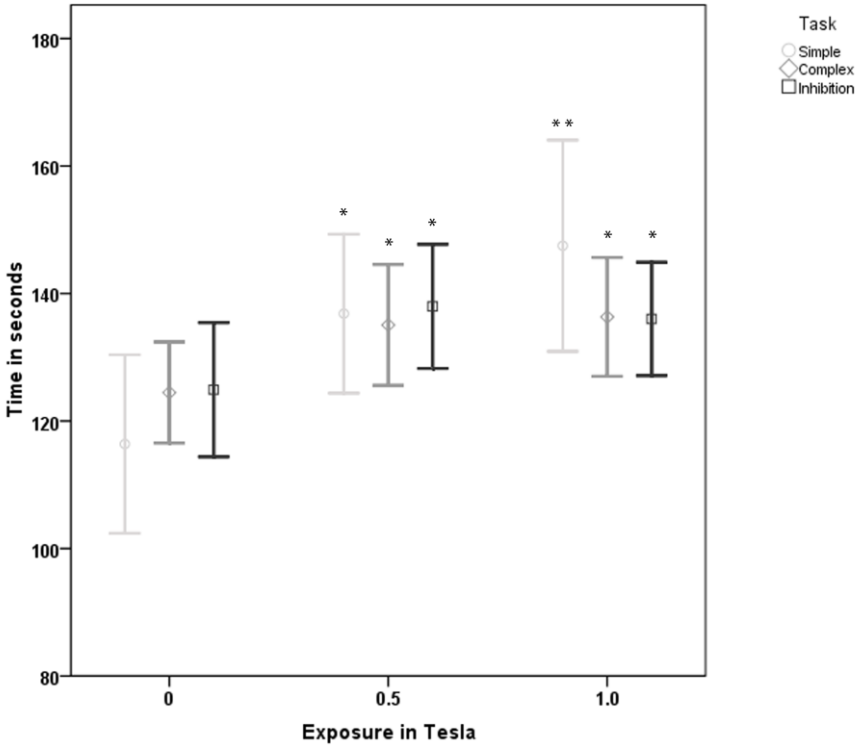

Figure 3 Disengagement time (time needed to release target button) in milliseconds on the three different levels of the reaction time task in the three conditions. Error bars represent 95% Confidence Interval of the mean. * Significant different from sham condition at p<0.05; ** significant different from sham condition at p<0.001, N=30

Table 2 Average test performance and standard deviations for each neurobehavioral test in the 0 (sham); 0.5 (low) and 1.0 T (high) exposure condition (N=30).

Test	Measure	Sham		Low		High	
		Mean	SD	Mean	SD	Mean	SD
RBMT	Immediate recall	10.1	3.4	10.3	3.2	9.8	2.5
	Delayed recall	9.5	3.3	9.2	3.0	8.6	2.8
	Difference in %	93.9	16.6	89.4	16.7	88.7	22.8
MCG	Immediate recall	35.7	0.7	35.6	0.7	35.7	0.6
	Delayed recall	20.8	4.8	21.8	5.4	21.3	5.4
	Difference (Δ)	14.9	4.6	13.8	5.4	14.4	5.1
Letter-number	Points 1[a]	45.6	16.4	48.0	17.3	45.1	20.3
	Points 2[a]	46.8	20.8	46.7	20.0	46.6	19.8
	Difference (Δ)[a]	-1.4	20.2	1.2	19.9	-1.6	15.0
Cancellation	Speed[b]	73.4	10.7	73.4	11.9	72.8	11.7
Reaction simple[h]	Reaction time[c,f]	331	41	330	34	329	32
	Motion time[d,f]	217	54	208	50	215	61
	Disengagement[e,f]	116	36	137	33	148	44
Reaction complex[h]	Reaction time[c,f]	395	45	393	41	387	35
	Motion time[d,f]	240	58	239	54	239	60
	Disengagement[e,f]	124	20	135	25	136	25
Reaction inhibition[h]	Reaction time[c,f]	443	55	427	51	435	43
	Motion time[d,f]	241	56	248	58	249	63
	Disengagement[e,f]	125	27	138	26	136	24
Roadmap	Time (sec)	50.2	20.7	50.1	23.3	49.4	20.8
JULO	Errors	2.4	2.1	1.3	1.7	2.2	2.1
Line bisection	Deviation (%)	100.3	6.7	100.6	7.1	101.0	7.0
Kappers task	Deviation in (°)	56.5	29.4	54.1	24.5	58.0	30.1
Visual tracking	Time (sec)	39.1	12.6	37.8	10.0	41.0	14.9
F.A.C.T.	1.5 cpd.	303.3	42.8	295.6	54.0	288.2	55.6
	3.0 cpd.	400.5	98.6	377.2	99.1	425.1	93.3
	6.0 cpd.	316.5	125.9	304.9	113.5	286.4	120.6
	12.0 cpd.	101.8	68.6	105.3	75.4	97.7	58.7
	18.0 cpd.	29.4	14.8	29.1	30.5	25.4	17.6
Pursuit aiming (S)	Speed[b]	148.0	13.9	148.2	14.1	149.9	16.0
	Precision[g]	81.5	7.3	81.9	8.0	79.9	8.5
Pursuit aiming (L)	Speed[b]	156.3	15.9	159.1	14.9	157.7	15.7
	Precision[g]	94.1	3.2	93.5	6.3	93.6	4.7

Abbreviations: (cpd.) Cycles per degree, (L) Large, (ms) Milliseconds (S) Small, (SD) Standard Deviation, (sec) Seconds. All data represent raw, untransformed data. [a] Points letter-number sequencing is defined as items of longest row multiplied by amount of correct recalled rows. [b] Speed is calculated as correct scored items in 60 seconds. [c] Reaction time is time release of home button after stimulus. [d] Motion time is time needed to go from home button to target button.

[e] Disengagement is time needed to release the target button. [f] Average of the median values.

[g] Precision is calculated as total correct responses divided by total amount of responses in 60 sec

[h] in milliseconds.

Table 3 Estimated trends of neurobehavioral test performance per 100 mT using a continuous mixed effects model adjusted for session, gender and ever experienced mild motion sickness symptoms (N=30).

Domain	Test	Measure	Inter-cept	β per 100mT	Lower CI	Upper CI	p
Memory	RBMT immediate	Words	10.5	-0.03	-0.14	-0.08	0.63
	RBMT delayed		9.9	-0.08	-0.18	0.02	0.12
	RBMT Δ in %		95.6	-0.74	-1.55	0.06	0.07
	MCG immediate	Points	35.7	-4.8E^{-3}	-0.04	0.03	0.76
	MCG delayed		23.5	0.05	-0.12	0.20	0.58
	MCG Δ		12.2	-0.04	-0.21	0.12	0.60
	Letter-numb 1	Points	50.9	-0.34	-0.71	0.64	0.92
	Letter-numb 2		46.0	0.08	-0.59	0.76	0.81
	Letter-numbΔ		5.1	-0.16	-1.08	0.76	0.73
Attention	Symbol cancel	Speed	77.4	-0.36	-1.46	0.74	0.52
	Reaction task-simple	Reaction	326	-0.08	-1.05	0.98	0.87
		Motion	208	0.27	-0.67	1.22	0.56
		Disengagement	124	2.74	1.58	3.90	**0.00**
	Reaction task-complex	Reaction	386	-0.77	-1.82	0.27	0.14
		Motion	235	0.29	-0.70	1.27	0.56
		Disengagement	122	1.17	0.40	1.95	**0.00**
	Reaction task-inhibition	Reaction	422	-0.50	-1.72	0.72	0.42
		Motion	233	1.17	-4.8 E^{-3}	2.35	**0.05**
		Disengagement	126	1.12	0.33	1.91	**0.01**
Spatial Orientation	Roadmap	Time [a]	42.1	2.1 E^{-4}	-2.7 E^{-3}	2.3 E^{-3}	0.87
	JULO	Errors [a]	2.1	-0.01	-0.02	3.8 E^{-3}	0.17
	Line bisection	Deviation [b]	101.5	0.07	9.6 E^{-4}	0.14	**0.05**
Haptic	Kappers	Deviation	53.8	0.14	-0.54	0.82	0.68
Visual	Visual tracking	Time [a]	34.4	1.3 E^{-3}	-1.9 E^{-3}	4.5 E^{-3}	0.43
	F.A.C.T.	1.5 [a]	309.0	-1.6 E^{-3}	-4.4 E^{-3}	1.3 E^{-3}	0.28
		3.0 [a]	416.9	2.8 E^{-3}	-2.2 E^{-3}	7.7 E^{-3}	0.27
		6.0 [a]	300.6	-2.8 E^{-3}	-9.6 E^{-3}	4.1 E^{-3}	0.42
		12.0 [a]	81.3	7.5 E^{-3}	-2.5 E^{-3}	0.02	0.14
		18.0 [a]	26.9	-0.01	-0.03	1.9 E^{-3}	0.09
Visuomotor	Pursuit aiming small	Speed	152.3	0.17	-0.19	0.53	0.36
		Precision	81.6	-0.15	-0.40	0.10	0.24
	Pursuit aiming large	Speed	162.7	0.15	-0.20	0.49	0.40
		Precision	94.8	-0.09	-0.25	0.07	0.26

Abbreviations: mT, milliTesla; CI, Confidence Interval. Significant values at p≤0.05 level are given in bold. [a] Back transformed results; analysis based on log10 transformed data. [b] Model was adjusted for session, gender, motion sickness *and* hand preference.

2.4 DISCUSSION

The main goal of this study was to investigate the acute effects movement-induced TVMF within a SMF from a 7 T MRI scanner on neurocognitive functioning. In the tested healthy population, we observed a significant exposure-response relationship, indicating a decrease in attention related to a reduced working memory and a decrease in visuospatial perception. Also in verbal memory functioning (story recall), a subtle decrease was seen, but this association did not reach statistical significance ($p=0.07$). These findings support the hypothesis that head movement in a spatially heterogeneous SMF up to 1.0 T does temporarily affect neurocognitive functioning. The current study design does not allow us to disentangle any effect to be associated only with SMF or TVMF or with the combination of both. In addition, the duration of any effect of motion-induced TVMF is unknown. Since it is not feasible to induce strong TVMF (by head movements) during the completion of a task, subjects performed head movements immediately before each single task. This implies that we would only pick up an effect of TVMF lasting longer than the duration of a single task (from 30 to 180 s). Our results show that effects due to TVMF would have to last for at least 90 s, that is, the longest task for which we found a statistically significant effect (reaction time task). This is longer than most other tasks except for the Kappers, memory and letter/number sequencing tasks which took up to 180 s and did not show significant effects of exposure.

The results as found in this study do not indicate a general effect of magnetic field exposure on neurocognitive functioning but show that rather specific target domains are affected. Analysis of the most fundamental neurocognitive functions of attention and concentration, like arousal, did not show an effect of exposure as tested by the symbol cancellation task and letter-number sequencing task. However, more specific aspects of attention and concentration showed that motion time was negatively affected in the inhibition reaction time task (+5.0% per Tesla exposure) meaning that participants moved slower from the home button to the target button during exposure compared with sham. Since we did not see a similar effect on the other two levels (simple and complex) of the reaction time tasks, this indicates that an increased motion time performance due to exposure might only occur when executing complex mental tasks. In the same reaction time task, disengagement time appeared to be increased on all three levels of the tasks when exposed to SMF and TVMF (ranging from +8.9 to +21.1% per Tesla exposure). This

end point reflects the time a subject needs to release the target button before returning to the home button, meaning putting one trial to an end. Attentional disengagement and task demand are both processed by working memory resources and require the coordination of information under executive control (Smallwood et al. 2006). In this way, an increased disengagement time reflects a cognitive- or attention-related error caused by an increased working memory activity (Cheyne et al. 2009). This can be concluded from the intercept values (in table 3), where disengagement time increases with increasing level of the task because more working memory is required. However, we did not observe an effect of magnetic field intensity on disengagement time by task level. Both increased motion time and increased disengagement time of the reaction time task suggest that when a high cognitive working load is required in a magnetic field, less working memory is available to keep the same level of attention and concentration.

In addition to the reaction time task, verbal memory performance as reflected by the Rivermead Behavioural Memory Test story recall (RBMT) reached borderline statistical significance ($p=0.07$). However, non-verbal memory performance was not affected by magnetic field exposure as shown by the Medial College of Georgia figure (MCG). De Vocht and colleagues (de Vocht et al. 2006a) earlier found both verbal and non-verbal memory to be affected by magnetic field exposure.

More specific neurocognitive domains exploring visual performance (F.A.C.T.), motor performance (visual tracking task) or an interaction between both (pursuit aiming task) did not show an effect of exposure, in contrast to previous findings (de Vocht et al. 2007b; de Vocht et al. 2006a; de Vocht et al. 2003). In addition, the registered motion time in the reaction time task had a visuomotor component as well. We only found an effect at the most difficult level, indicating that the found effect is more related to working memory than to visuomotor performance.

Based on the questionnaire after each session, in the sham, low and high exposure condition, 4, 10 and 19 subjects, respectively, reported sensory symptoms. For example, in the highest exposure condition, a metallic taste (12 subjects) was most commonly reported followed by dizziness (six subjects), headache (five subjects) and nausea (one subject). Domains related to dizziness and nausea like visuospatial performance suggested that exposure to magnetic fields affects performance on the line bisection task ($p=0.05$). Subjects demonstrated a subtle but significant changed

perception of the true middle of the line, corrected for handedness. In the sham condition, our subjects scored around the true middle of the line, while exposure to SMF and TVMF significantly increased deviation to the right (+46.7% per Tesla exposure). As described in the previous studies, normal subjects bisect lines slightly to the left (-1.6%) from the true center of the line irrespective of hand preference (Bradshaw et al. 1985; Scarisbrick et al. 1987). In this regard, subjects in our study performed above expectation in the sham condition. However, in the exposure conditions, deviation shifted in the opposite direction of those described for normal subjects above. The direction of deviation might be influenced by the position of the subject with respect to the magnetic field lines (Houpt et al. 2003). de Vocht et al (de Vocht et al. 2007b) used an adapted line bisection task with random orientated lines and found a trend for an increased deviation at exposure of 1.6 T and 300 mT/s. Other tasks examining visuospatial performance like the judgement of line orientation and the roadmap did not show an effect.

This study demonstrates that attention, concentration and visuospatial orientation are affected by exposure to MRI-related static and time-varying magnetic fields. Alternatively, the effects on neurocognitive functioning could be influenced by a fluctuation in motivation or attentional span instead of an effect that can be attributed to the exposure conditions. However, we did not find a difference in performance for the WAIS-III Letter-number sequencing task when administered at the beginning versus later in the test battery in the sham condition.

De Vocht and colleagues (de Vocht et al. 2007b; de Vocht et al. 2006a; de Vocht et al. 2003) showed in earlier studies an association between exposure to SMF and TVMF and a lowered visuomotor performance and visual perception. In these experiments, the F.A.C.T., pursuit aiming and visual tracking task were affected, while these tasks were not affected in our experiment. Although our results did not corroborate earlier findings on these specific tasks, the same domains of vision and more basal cognitive functions seemed to be affected by exposure in our experiment. Differences in experimental method between experiments complicate comparisons and could have contributed to the differences in results. For example, in the current experiment, exposure levels of the TVMF were estimated at least four times higher (300 compared with 1200 mT/ s) due to faster head movements over a larger angle and in two directions. In addition, we used a double blind test design to prevent potential bias due to knowledge about the exposure condition. Furthermore, the previous experiments might have included more vulnerable groups, where we used a

much younger and more homogeneous group of subjects and excluded those with a history of motion sickness. Therefore, it is conceivable that only high distinctive and sensitive tests for visuomotor performance and visual perception might have been able to reveal effects of exposure in this experiment.

Although we assumed in our main analysis a linear association between SMF exposure and test performance, we realize that neurocognitive functions do not necessary have to respond in this way since individual and clusters of neurons have diverse activation and saturation thresholds. Therefore, we also analyzed the data by use of a categorical exposure model, showing that the results did not appreciably differ from the continuous analysis (data not shown). The number of exposure conditions was too limited to pursue more sophisticated nonlinear exposure-response modelling.

Strengths of this study include a balanced double-blind randomized crossover design that eliminates errors since neurocognitive tests in healthy subjects are highly influenced by age, gender and educational level. In this design, individuals served as their own controls. We set out to perform a double-blind experiment by using similar tents, blind guiding of subjects and test leaders into the tents and use of MRI audio recordings in the sham condition. However, blinding was not perfect since four subjects reported that they could feel the magnetic fields because they had a splint behind their teeth that was in some cases made of a weak paramagnetic material, undetected by the metal detector. Post-hoc sensitivity analyses excluding these subjects did not show notably different results. Based on the post-session questionnaires, perceived 'exposure' or 'no exposure' by the remaining 26 subjects in the sham, 0.5 and 1.0 Tesla exposure condition was correct in 69%, 38% and 65% of the sessions, respectively. Test leaders were asked to indicate 'sham', 'low' or 'high' exposure and had 93%, 62% and 42% correct predictions in the 0, 0.5 and 1.0 Tesla conditions, respectively. However, these rates for test leaders are more difficult to interpret since a device they needed for a test at the very end of the session contained some magnetic material, which could reveal the exposure condition. Thus, blinding of the experiment in further studies can probably be improved by refining the setup and specifically enquire about magnetic splints prior to enrolment.

Overall, the results of this study show that neurocognitive functioning is acutely affected when exposed to strong TVMF due to head movements within a SMF. Domains that were affected include attention/concentration and visuospatial orientation and possibly long-term memory. However, the exact implications and

mechanisms of these subtle acute neurocognitive effects in practical settings remain unclear. In future research, it will be of interest to focus more on different neurocognitive domains under high working memory load and to differentiate between effects raised by either the SMF or the time-varying magnetic fields or the combination of both. A better understanding of the mechanisms causing acute effects can be used as a basis for design of relevant control measures to lower exposure and reduce the occurrence of neurobehavioral effects for individuals employed under these conditions.

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SUPPLEMENTAL MATERIAL

Table S1 Included neurocognitive domains and matching test from the used test battery with measured variables.

Domain	Neurocognitive test	Variables/ Parameters
Memory	Long term memory story recall (RBMT)	Amount of correct words (max. 21)
	Long term memory picture recall (MCG)	Amount of correct drawn lines (max. 36)
	Letter-number sequencing task (WAISIII)	Length of last repeated sequence multiplied by amount of correct recalled rows
Attention	Symbol cancellation task	Speed (correct cancelled items in 60 seconds)
	Reaction time task (simple, complex and inhibition)	Reaction time Motion time (time to go from home to target button) Disengagement time (time needed to release target button)
(Spatial) Orientation	Roadmap task	Time to complete task
	Judgment of Line Orientation task (JULO)	Correct judged lines (max. 30)
	Line bisection task	Deviation as percentage from centre of the line
Haptic perception	Kappers task	Absolute deviation in degrees
Visual field	Visual tracking task	Tracking speed
	Contrast sensitivity (F.A.C.T.)	Contrast sensitivity level in cycles per degree
Visuomotor performance	Pursuit Aiming task	Speed (correct cancelled items in 60 seconds) Precision (correct responses divided by the total amount of responses in 60 seconds)

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Chapter 3

Does assessment of personal exposure matter during experimental neurocognitive testing in MRI-related magnetic fields?

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ABSTRACT

To determine whether the use of quantitative personal exposure measurements in experimental research would result in better estimates of the associations between static and time-varying magnetic field exposure and neurocognitive test performance than when exposure categories were based solely on distance to the magnetic field source. In our original analysis, based on distance to the magnet of a 7 T MRI scanner, an effect of exposure to static magnetic fields was observed. We performed a sensitivity analysis of test performance on a reaction task and line bisection task with different exposure measures that were derived from personal real-time measurements. The exposure measures were highly comparable, and almost all models resulted in significant associations between exposure to time-varying magnetic fields within a static magnetic field and performance on a reaction and line bisection task. In a controlled experimental setup, distance to the bore is a good proxy for personal exposure when placing subjects at fixed positions with standardized head movements in the magnetic stray fields of a 7 T MRI. Use of a magnetic field dosimeter is, however, important for estimating quantitative exposure response

3.1 INTRODUCTION

With the increased use of MRI scanners up to 9.4 Tesla (T) (Health Protection Agency 2008), possible biological effects of exposure to the strong magnetic fields became a major topic. With respect to neurocognitive functions, experimental studies performed in the stray fields around the bore have reported statistically significant negative effects of exposure to a combination of static magnetic fields (SMF) and time-varying magnetic fields (TVMF) on spatial orientation and attention and concentration (de Vocht et al. 2003; de Vocht et al. 2006b; van Nierop et al. 2012). However, experimental studies performed within the bore without scanning, reported no significant cognitive effects of exposure to SMF or the combination of SMF and TVMF (Chakeres et al. 2003; Gilles et al. 2013; Heinrich et al. 2013; Lepsien et al. 2012). As a consequence, consensus on the cause of these effects has not been reached, although occupational exposure levels associated with these strong SMF from MRI are regarded as safe (ICNIRP 2009).

One of the major challenges within these experimental studies is the exact characterization of exposure to SMF and TVMF. Inside the homogeneous SMF of the MRI scanner exposure can be reliably assessed. However, toward the edges of the bore and around the magnet the fields are very inhomogeneous due to the steep gradients that are present, exposure can therefore vary considerably over short distances. Even in a controlled experimental setting, it is difficult to estimate personal exposure within such inhomogeneous stray fields without the use of a measurement device, since exact spatial position and speed of movement are very important factors affecting exposure. Consequently, previously observed negative effects of exposure on cognitive functions may be a result of poor exposure estimates.

Accurate and precise measurement devices to assess personal exposure to magnetic field strength were unavailable until recently. In previous human experiments, exposure measures for SMF and TVMF have been based on; field line maps as provided by the manufacturers of the system that show the spatial distribution of the magnetic flux densities (de Vocht et al. 2006a; Lepsien et al. 2012; Roberts et al. 2011), manually built devices (de Vocht et al. 2007; de Vocht et al. 2003), Hall sensors (Heinrich et al. 2013), a Gauss meter (van Nierop et al. 2012), or a prototype dosimeter (de Vocht et al. 2009). In addition, computer models are often used to estimate personal exposure to TVMF (Hartwig et al. 2011; Trakic et al. 2007). Recently, a personal measurement device capable of measuring strong static

magnetic fields and time-varying magnetic fields has been developed (Magnetic Field Dosimeter, University of Queensland, Australia (Fuentes et al. 2008).

In a recent experimental study (van Nierop et al. 2012), we employed this device to investigate whether quantitative measurements of personal exposure to magnetic fields in experimental research would result in a better estimate of the associations between SMF and TVMF exposure and neurocognitive test performances. To this end, we performed a sensitivity analysis on selected cognitive tasks that previously showed a significant association with assigned exposure—that is, when exposure measures were based on predefined distances to the scanner bore by stationary measurement (van Nierop et al. 2012).We modeled different measures of personal exposure from the measurement data obtained during the experiment. In addition, we evaluated the standardized head movement protocol that was used to repeatedly induce similar levels of TVMF within the static magnetic stray field.

3.2 METHODS

Experimental design

A group of 31 healthy volunteers who were unfamiliar with MRI were tested in a double-blind randomized crossover design. The group consisted of 10 male and 21 female subjects with an average age of 23.8 years (standard deviation, 6.4 years). To double-blind the experiment, the subject and experimenter were blindly guided into a tent. Each subject was tested on three occasions with 1 week in between. The low and high exposure conditions were located in the static magnetic stray fields of a passively shielded 7.0 T Philips Achieva MRI system located at the Utrecht Medical Center. The sham condition (<42 mT) was located outside the scanner room. The sequence of exposure was balanced and the order was randomly assigned to each subject before the start of the experiment.

The neurocognitive test battery consisted of 12 neurocognitive tasks and took on average 60 min to complete. In addition to the SMF already present, TVMF exposure was elicited by having volunteers made standardized head movements before every single task: 10 head movements were made in the horizontal direction, and 10 head movements were made in a vertical direction (covering an angle of 180 degrees in 0.8 s). The start of each movement was indicated by an auditory cue.

In the current study, we report only on cognitive tasks that showed a statistically significant effect of exposure in the original study. These were observed for spatial orientation by use of a line bisection task (see Schenkenberg et al. in (Lezak et al. 2004)) in which 20 horizontal lines with different line lengths had to be bisected in the middle. The (percentage of) deviation from the middle of the line was increased, meaning that subjects bisect lines more to the right side when exposed. In addition, attention/ concentration was significantly affected as measured by a simple, complex, and inhibition reaction task (van Zomeren et al. 1987; van Zomeren et al. 1984). Subjects had to respond to one light (simple task) out of nine lights (complex task) that started burning and press the target button (left of the burning light in the inhibition task) as quickly as possible. Motion time (time between start of light burning and contact with the target button) and disengagement time (time between release of the target button and return to the "home" button) were significantly increased when exposed. The line bisection task was performed on average after 18 min of exposure and the three different versions of the reaction task after 44, 46, and 49 min of exposure, respectively. A description of the other 10 neurocognitive tasks that showed no effect of exposure can be found elsewhere (van Nierop et al. 2012). The study was approved by the local medical ethics committee of the University Medical Center in Utrecht.

Exposure assessment methods

In the original analysis (van Nierop et al. 2012), exposure was classified as low and high (estimated to be 500 mT and 1000 mT, respectively) based on the distance of the subject from the MRI magnet. A three-axis Hall Magnetometer (Metrolab THM 1176) was used to identify the locations within the magnetic stray fields of the MRI system that had magnetic field densities of 500 mT and 1000 mT. Measurements were taken at the presumed dosimeter location at head height in sitting position of 150 cm. During the experiment, the subject sat on a chair that was fixed to the prescribed locations, with his or her back toward the bore of the MRI system.

For the sensitivity analysis, personal exposure to magnetic fields was registered in real-time during each session of the experiment with a dosimeter (Magnetic Field Dosimeter, University of Queensland, Australia) that was attached to the inside top of a plastic helmet worn by the subject. The dosimeter registered exposure to static magnetic fields (with a sampling rate of 20 Hz) and time-varying

magnetic fields (with a sampling rate of 10 kHz) in three directions, where the total static magnetic field is

$$|B| = \sqrt{B_x^{\,2} + B_y^{\,2} + B_z^{\,2}} \quad \text{and} \qquad [1]$$

and the total time-varying magnetic field is

$$|dB/dt| = \sqrt{(dB_x/dt)^2 + (dB_y/dt)^2 + (dB_z/dt)^2} \qquad [2]$$

Data analysis

Dosimeter measurement data were first checked for out-of- range values and inconsistencies. Two experimental sessions were removed since out-of-range peaks in SMF and TVMF were recorded. The data for these two adjacent sessions were collected with the same dosimeter, suggesting that there may have been a problem with that particular dosimeter on that specific day.

Start and end times of each set of head movements and periods of task performance were identified by visual analysis of the personal exposure profiles (an example is given in Fig. 1). Time-weighted average exposure during head movements and task performance were estimated based on the dosimeter readings over these identified time slots as well as over an entire session. Cumulative exposure was calculated using the area under the curve up to the specific task.

From the dosimeter readings, four different measures were derived for SMF and TVMF separately:

1. Average exposure over one entire session of cognitive testing (~60 min) expressed as the time-weighted average exposure.
2. Exposure during head movements prior to the specific neurocognitive task expressed as the time-weighted average exposure. These time slots were presumably the periods of highest exposure to both SMF and TVMF.
3. Exposure during performance of a specific neurocognitive task. Presumably, SMF were the only type of magnetic fields present, as subjects sat still during task performance.
4. Cumulative exposure over the session up to but not including the specific neurocognitive task.

Statistical analysis was performed to calculate the correlation coefficients between the different exposure measures. Analysis of variance was performed to define the standardization of head movement protocol. To analyze the effect of different exposure measures on test performance, a linear mixed model was used to estimate the intercept and regression coefficient of the model. Within this sensitivity analysis, each of the exposure measures were separately entered as a continuous exposure variable in a linear mixed effects model assuming linear exposure-effect associations. In line with the original analysis, all sensitivity analyses were adjusted for session number, gender, and report of "ever experienced mild symptoms of motion sickness" (yes versus no). The line bisection task was additionally adjusted for handedness. The volunteers were modeled as random effects using heterogeneous compound symmetry, which assumes similar correlation between observations of the same subject but no correlation between different subjects. Statistical significance level was defined as $P \leq 0.05$. For comparison between models values of the Akaike Information Criterion (AIC) were estimated.

The limit of detection (LOD) of the dosimeter was set to 42 mT for SMF and 37 mT/s for TVMF. This was based on the maximum value obtained among 500 measurements of situations with no exposure (data not presented). Consequently, it was not possible to identify time intervals of head movements, task performance, and cumulative exposure up to the task in the sham condition. Therefore, in the main analyses, sham exposure values were set to the value of the $LOD/\sqrt{2}$. Applying alternative measures in the sham condition such as the original mean personal measured values or LOD/2 did not meaningfully change the results (data not shown).

Descriptive statistics, exposure measures, correlations, and analyses of variance were calculated using SAS (version 9.2; SAS Institute Inc., Cary, North Carolina, USA). Statistical analyses of inter- and intra-individual differences in test performance in association with exposure measures were performed with mixed-effects models using SPSS (version 20.0; IBM SPSS Statistics).

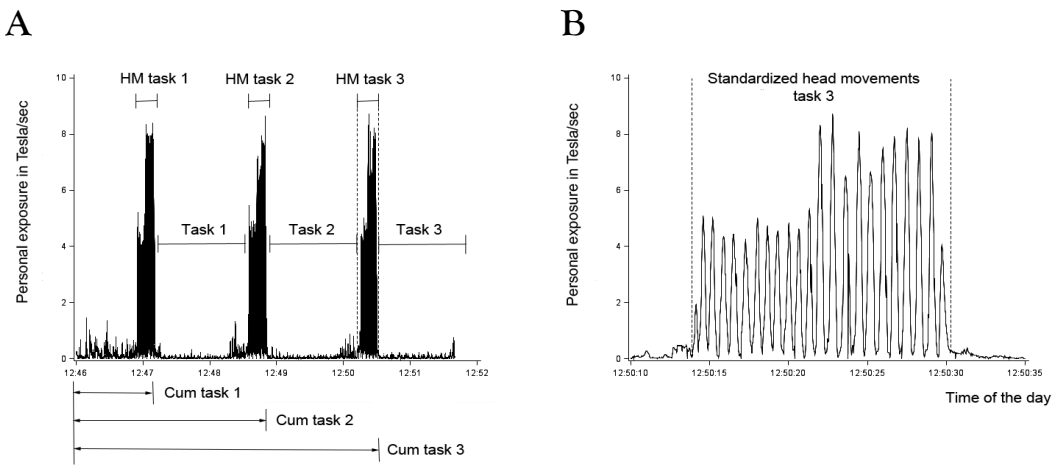

Figure 1 Recording from a personal dosimeter of a subject in a 1000 mT condition during the experiment. Sum of personal exposure in x-,y- and z-direction is depicted for TVMF (A). Head movements consisted of 10 movements in horizontal direction (forth and back) followed by 10 movements in vertical direction (enlarged in panel B). They were defined by start of the sinus waves until the end of the sinus wave. Task performance was defined as the period between two head movement periods. Cumulative exposure was defined as the area under the curve up till the specific task.

3.3 RESULTS

Thirty subjects completed all three test sessions resulting in 90 observations. The line bisection task had 86 observations (3 missing exposure and 1 missing outcome data) and the reaction task had 85 observations (2 missing exposure and 3 missing outcome data).

Measured time-weighted average exposure to SMF in the low exposure category over the entire session, during head movements or during task performance, varied between 79% and 115% of the distance-defined exposure value of 500 mT (Table 1). In the high exposure category, the exposure varied between 61% and 101% of the estimated 1000 mT value.

The average exposures to TVMF during the head movements were 1400 and 2400 mT/s for the low and high exposure condition, respectively (Table 1). During task performance, the average exposure to TVMF was almost negligible at around 55 and 80 mT/s in the low and high exposure condition, respectively. However, these levels are still significantly different from each other due to relatively small standard deviations of the distributions in the low and high exposure condition. When

TVMF exposure was averaged over the entire session, encompassing both low (tasks performance) and high (head movements) exposure periods that occurred during each exposure condition, the resulting TVMF exposures were 208 and 365 mT/s for the low and high exposure condition, respectively. Cumulative exposure to SMF and TVMF, as calculated from the start of a session until the start of a particular task, was much higher for the line bisection task compared with the reaction tasks. The reason for this was that the line bisection task took place well before the reaction tasks at 18 and 44 min, respectively. The correlations between different exposure measures (entire session, during head movements, during task performance, and cumulative exposure) for SMF and TVMF were moderate to very high (range, 0.63–0.99) for the simple reaction task and high to very high for the complex reaction task (range, 0.71– 0.99), inhibition reaction task (range, 0.71–0.99), and line bisection task (range, 0.77–0.99) (data not shown).

Figure 2 shows the range of average personal exposure in the sham and the low and high exposure condition for the SMF and TVMF exposure measures in the inhibition reaction task. The time-weighted average exposure to SMF during the entire session (Fig. 2A), during head movement (Fig. 2C), and during task performance (Fig. 2E), differed only very slightly from each other. The average exposure during head movements (Fig. 2C) was only marginally higher than the average over the entire session (Fig. 2A) and the latter was, in turn, slightly higher than the exposure during task performance (Fig. 2E). As expected, the time-weighted average exposure to TVMF over the entire session (Fig. 2B) and during task performance (Fig. 2F) was negligible. Only during head movements was the exposure to TVMF significantly higher (Fig. 2D).

Individual average exposures to SMF and TVMF during each of the head movements are shown in Figure 3. Analysis of variance showed that the within subject variance appeared to be even smaller than the between subject variance in the low and high exposure condition for both SMF and TVMF exposure (Table 2).

Results of the mixed model analysis of the inhibition reaction task on disengagement time using distance-defined assigned categories and personal exposure measures are shown in Table 3. With the exception of the TVMF exposure during a task, the AIC, intercept, and regression coefficients are highly comparable to the original exposure category based on assigned distance to the bore only. When comparing the exposure measures, it should be taken into account that estimates, regression coefficients, and corresponding confidence intervals are not comparable

between all models, since the interval ranges of the exposure proxies differed in level and range. However, regression coefficients and corresponding confidence intervals can be compared within each category of SMF, TVMF, and cumulative exposure. AIC and P values, however, could be compared directly across all models. Results of the line bisection, simple reaction task, and complex reaction task showed similar effect associations and can be found in the Supporting Information.

Table 1 Time-Weighted average personal SMF exposure and TVMF exposure in the Low and High exposure conditions per task (n=30)

		SMF Exposure (in mT)						TVMF exposure (in mT)					
		Low			High			Low			High		
		Mean	GM	GSD	Mean	GM	GSD	Mean	GM	GSD	Mean	GM	GSD
	Entire session	464	460	1.15	774	768	1.13	208	205	1.20	365	360	1.18
During head movements	Simple RT	573	568	1.15	1000	989	1.16	1408	1385	1.21	2439	2415	1.16
	Complex RT	575	570	1.14	993	984	1.16	1413	1392	1.20	2434	2410	1.15
	Inhibition RT	559	551	1.19	997	986	1.17	1347	1309	1.30	2435	2407	1.17
	LB	577	574	1.12	1007	996	1.16	1401	1380	1.19	2469	2437	1.18
During task	Simple RT	409	405	1.17	666	660	1.15	51.8	49.3	1.37	70.8	68.3	1.30
	Complex RT	411	407	1.16	671	665	1.15	53.3	51.3	1.32	80.0	77.3	1.29
	Inhibition RT	394	389	1.16	611	605	1.15	57.4	55.4	1.34	99.9	97.0	1.29
	LB	430	426	1.15	702	697	1.13	64.2	61.5	1.33	98.1	65.6	1.26
Cumulative	Simple RT	1251	1237	1.17	2015	1987	1.19	561	555	1.16	942	932	1.17
	Complex RT	1326	1313	1.16	2100	2072	1.18	595	588	1.17	990	980	1.16
	Inhibition RT	1382	1369	1.16	2188	2159	1.18	625	618	1.17	1040	1029	1.16
	LB	542	528	1.27	863	849	1.20	236	232	1.21	400	396	1.16

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; RT, reaction task. Sham exposure was below the level of detection.

Eighty-five observations were used for the reaction tasks and 86 observations were used for the line bisection task.

*Cumulative exposure up to the respective task is given in T·s for SMF and T·s^2 for TVMF.

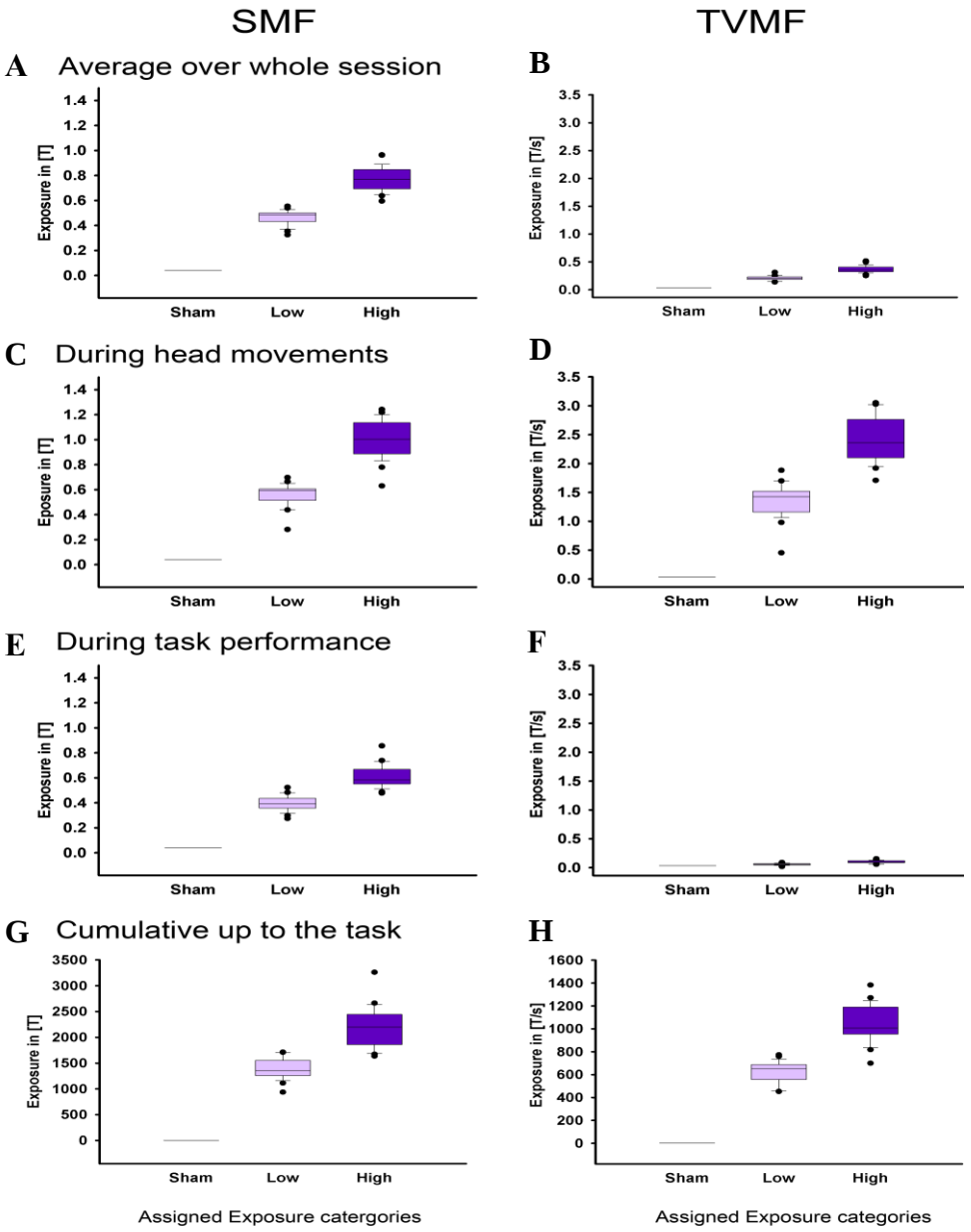

Figure 2 (A-H) Box and whisker plots of average personal exposure in the sham, low and high condition. 75 single subject exposure measurements are used per graph (28 in sham, 28 in low, 29 in high condition). The median value is given by the horizontal line in the box. The lower and upper whiskers reflect the 5th percentile and 95th percentile respectively. The graphs of exposure 'during head movements', 'during task performance' and 'cumulative up to the task' are specific for the inhibition reaction task (C-H).

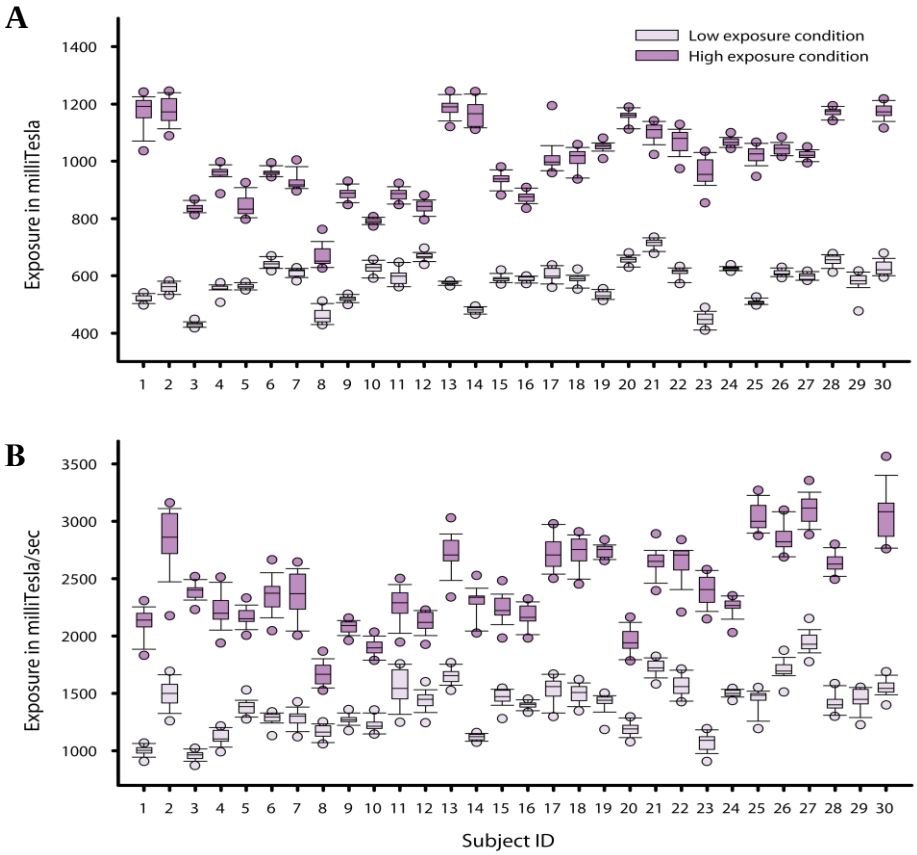

Figure 3 (A+B) Box and whisker plots of each single subject (N=30) when exposed to SMF (A) and TVMF (B) during each series of head movements (N=19). The median value for each subject is given by the horizontal line in the box. The lower and upper whiskers reflect the 5th percentile and 95th percentile respectively. Note: the high exposure condition of subject 29 is missing.

Table 2 Results of analyses of variance of average exposure during each head movement for the low and high exposure condition for SMF and TVMF (N=30)

Condition	Field	Subjects	Variance	%	Ratio95*
Low	SMF	Within	0.0027	14.8	1.22
		Between	0.0153	85.2	1.62
	TVMF	Within	0.0038	12.1	1.27
		Between	0.0276	87.9	1.92
High	SMF	Within	0.0009	4.2	1.12
		Between	0.0203	95.8	1.75
	TVMF	Within	0.0027	10.4	1.23
		Between	0.0232	89.5	1.82

* Ratio of the 2.5% and 97.5% of the within and between individual exposure distribution

Table 3 Results of the mixed model analyses of the inhibition reaction task on disengagement time (in milliseconds) using distance-defined assigned exposure categories and personal exposure in a continuous exposure model (K=30; N=85).

Exposure	AIC	Intercept	Beta	CI lower	CI higher	p-value
Assigned[a]	729.9	126.36	1.16	0.36	1.96	0.006
Session SMF[b]	729.9	125.58	1.49	0.40	2.58	0.008
HM SMF	729.8	125.59	1.20	0.37	2.03	0.006
Task SMF	729.4	125.34	1.90	0.51	3.29	0.008
Session TVMF[b]	726.4	124.14	3.71	1.34	6.08	0.003
HM TVMF	731.0	125.84	0.58	0.17	0.82	0.004
Task TVMF	728.1	124.21	12.12	0.40	23.83	0.043
Cum SMF	746.4	126.34	$4.77\ E^{-4}$	$1.17\ E^{-4}$	$8.37\ E^{-4}$	0.010
Cum TVMF	742.8	125.36	$1.16\ E^{-3}$	$4.14\ E^{-4}$	$1.91\ E^{-3}$	0.003

Abbreviations: AIC, Akaike Information Criterion; Assigned, assigned categories; Session, average exposure over whole session; HM, during head movements before specific task; Task, during task performance; Cum, cumulative exposure up to this task; SMF, Static Magnetic Field exposure; TVMF, Time-varying magnetic field exposure. For the sham, low, and high exposure conditions, 28, 28, and 29 observations were available, respectively.

[a]Distance-defined assigned categories

[b]Average exposure over entire session

3.4 DISCUSSION

In this study, we compared the results obtained with distance-defined positions and personal exposure during a series of experiments investigating the effect of MRI-related SMF and TVMF exposure on neurocognitive test performances. Similar associations between exposure and neurocognitive test performance were found when using quantitative personal exposure measurements collected with a dosimeter compared with those based on distance to the bore of the MRI system as identified by a magnetometer.

The average measured exposures were generally close to what was expected for these categories as can be seen for the exposure estimates during head movements and task performance (Table 1). The discrepancies between measured personal SMF exposure values and distance-defined assigned SMF exposure were larger during task performance than during head movements and were more marked during task performance in the high exposure versus the low exposure condition (Table 1). Both can be explained by certain practical details of the experiment. First, during the head movements, subjects sat upright (with the dosimeter attached to their helmet) with their heads closer to the bore and the marker at a height of 150 cm, where the magnetometer readings were taken. This resulted in very good agreement between the predicted predefined SMF exposure of 500 and 1000 mT and the measured personal exposure values during head movements. However, while performing a task, subjects leaned forward, away from the bore and the marker toward the table, resulting in lower SMF exposure levels in both exposure conditions. Second, in the high exposure condition, subjects were at the edge of the scanner bore where the gradient fields are considerably steeper than in the low exposure condition: a smaller change in distance as the subjects moved forward in the high condition therefore had a relatively larger impact on exposure level than a similar movement in the low condition.

The small within-subject variance in exposure indicates that subjects had similar exposure during each series of head movements (covering an angle of 180 degrees in 0.8 s) within a session, and underscores the effectiveness of the standard protocol for standardizing head movements that was used to ensure that similar levels of TVMF were repeatedly induced. Although one subject (Fig. 3, subject 8) had in the high exposure condition a magnetic field exposure in the range of the low exposure condition, the exposure in the low exposure condition was also

considerably lower for this subject compared with that of the other. As a result, exposure categories were still distinctive from each other.

Furthermore, since small changes in a strong heterogeneous magnetic stray field can lead to considerable changes in exposure, we analyzed the effect of personal height on measured exposure. No effect was detected, most likely due to the fact that differences in personal height were relatively small (range, 154–200 cm; interquartile range, 9.25) and differences in position of the head would actually have been smaller, since tasks were performed seated.

Comparing the results of the different exposure assessment models shows that the AICs of models with exposure based on distance to the magnet were comparable to those where personal exposure was modeled (Table 3). Only the model of TVMF exposure during task performance resulted in a poor fit expressed by a large confidence interval and a high p-value. This is mainly caused by very low exposure, since there was hardly any movement of the head during task performance. However, cumulative exposure to SMF and to TVMF from the start up to the specific task yielded the weakest fit of all models, as reflected by the high AIC values, since exposure during task and head movements up to that specific task were averaged.

Based on our analyses, it would appear that these two different types of exposure assessments and their resulting measures of exposure do not influence the outcome of the experiments. This suggests that the differences in outcomes between earlier performed research studies, inside and outside the scanner bore, cannot be explained by the exposure method used (assuming that the data were collected reliably, positioning was done properly, and movements were standardized). An explanation for the difference in effects should rather be sought in the divergence of the magnetic field lines and experimental setup used (e.g., subject population, field strengths, duration of exposure, direction of the magnetic fields, and choice of cognitive tasks). Nonetheless, in some research areas (e.g., those requiring estimates of real-life exposure), the use of a personal dosimeter has important additional value. Accurate estimates of in situ exposure to SMF and TVMF are very difficult to obtain without employing personal dosimeters, because differences in walking speed or a difference in position of a few centimeters from the exposure source can lead to considerable differences in exposure levels. This is especially true as one gets closer to the edge of the bore of MRI scanners with high magnetic field strengths, as was seen in this experiment. Radiographers, technicians, surgeons, and cleaning staff

working in the MRI room have different activities, movement patterns, locations, and durations of activities in the MRI room that will determine their exposures to SMF and TVMF. These exposures by definition will vary in intensity over a working day and between working days. There will be also a host of workplace factors that influence personal exposure, including magnetic field strength, design of the scanner, shielding of the magnet, steepness of the gradient field (density of field lines), and direction of field lines. All of these factors can lead to considerable variation in exposure levels within and between workers and occupational groups. Capturing this type of variation can be important for epidemiological and occupational risk assessment studies, and it is easier to assess this variation using personal dosimeters. Therefore, application of personal dosimeters will enable a more accurate description of quantitative exposure-response associations in epidemiological occupational studies and result in more accurate occupational exposure standards for technicians and others working around MRI systems. This is not as easy to achieve using semi-quantitative exposure assessment methods, such as those based on distance from and time spent around an MRI scanner.

However, for studies with a controlled experimental setup where exposure conditions and movements are strictly standardized and distinct exposure categories can be established (e.g., based on distance to the bore), semi-quantitative estimation of exposure is more straightforward than collecting personal exposure measurement using dosimeters.

ACKNOWLEDGEMENTS

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SUPPLEMENTAL MATERIAL

Table S1 Results of the mixed model analyses of the line bisection task using assigned exposure categories and personal exposure in a continuous exposure model (K=30; N=85).

Exposure	AIC	Intercept	Beta	CI lower	CI higher	P
Assigned	27053.3	101.44	0.06	-7.6 E^{-3}	0.13	0.080
Session SMF	27050.7	101.30	0.11	0.01	0.20	0.024
HM SMF	27051.3	101.28	0.08	0.01	0.15	0.023
Task SMF	27048.6	101.17	0.14	0.04	0.24	0.008
Session TVMF	27048.4	101.19	0.26	0.05	0.46	0.015
HM TVMF	27051.2	101.23	0.04	0.01	0.07	0.007
Task TVMF	27050.1	101.39	0.47	-0.54	1.47	0.363
Cum SMF	27065.7	101.37	8.15 E^{-5}	4.54 E^{-6}	1.58 E^{-4}	0.038
Cum TVMF	27063.0	101.29	2.05 E^{-4}	3.41 E^{-5}	3.77 E^{-4}	0.019

For the Sham 29, low 29 and high 28 subject observations were available.

Table S2 Results of the mixed model analyses of the simple reaction task on disengagement using assigned exposure categories and personal exposure in a continuous exposure model (K=30; N=85).

Exposure	AIC	Intercept	Beta	CI lower	CI higher	P
Assigned	794.8	124.13	2.75	1.55	3.95	0.000
Session SMF	794.8	122.43	3.63	2.03	5.24	0.000
HM SMF	796.0	122.93	2.73	1.50	3.97	0.000
Task SMF	794.0	121.69	4.30	2.44	6.16	0.000
Session TVMF	793.7	120.60	7.89	4.39	11.40	0.000
HM TVMF	797.8	123.57	1.09	0.60	1.58	0.000
Task TVMF	798.7	112.11	43.79	14.59	73.00	0.004
Cum SMF	811.4	124.66	1.29 E^{-3}	7.06 E^{-4}	1.87 E^{-3}	0.000
Cum TVMF	809.1	123.35	2.81 E^{-3}	1.58 E^{-3}	4.04 E^{-3}	0.000

For the Sham 28, low 28 and high 29 subject observations were available.

Table S3 Results of the mixed model analyses of the complex reaction task on disengagement time using assigned exposure categories and personal exposure in a continuous exposure model (K=30; N=85).

Exposure	AIC	Intercept	Beta	CI lower	CI higher	P
Assigned	719.8	121.68	1.22	0.44	2.00	0.003
Session SMF	719.5	120.84	1.61	0.56	2.66	0.003
HM SMF	721.2	121.35	1.16	0.34	2.98	0.006
Task SMF	719.3	120.76	1.85	0.63	3.07	0.004
Session TVMF	718.2	120.25	3.52	1.19	5.86	0.004
HM TVMF	722.7	121.91	0.46	0.15	0.78	0.005
Task TVMF	719.6	119.74	15.21	-0.37	30.79	0.056
Cum SMF	736.7	121.91	5.15 E^{-4}	1.50 E^{-4}	8.80 E^{-4}	0.007
Cum TVMF	734.8	121.53	1.13 E^{-3}	3.49 E^{-4}	1.91 E^{-3}	0.005

For the Sham 28, low 28 and high 29 subject observations were available.

Table S4 Results of the mixed model analyses of the inhibition reaction task on motion time using assigned exposure categories and personal exposure in a continuous exposure model (K=30; N=85).

Exposure	AIC	Intercept	Beta	CI lower	CI higher	P
Assigned	820.7	233.81	1.27	0.11	2.43	0.033
Session SMF	821.5	233.88	1.44	-0.15	3.03	0.075
HM SMF	822.6	234.71	1.00	-0.23	2.22	0.108
Task SMF	820.3	232.96	2.02	0.02	4.03	0.048
Session TVMF	820.4	234.01	2.93	-0.62	6.48	0.104
HM TVMF	824.6	235.27	0.39	-0.10	0.87	0.117
Task TVMF	816.8	230.62	15.34	-1.25	31.92	0.069
Cum SMF	837.7	234.52	4.62 E^{-4}	-0.61 E^{-5}	0.99 E^{-3}	0.082
Cum TVMF	836.4	234.73	9.38 E^{-4}	-1.80 E^{-4}	2.06 E^{-3}	0.098

For the Sham 28, low 28 and high 29 subject observations were available.

Abbreviations table S1-4:

Assigned	Assigned categories
Session	Average exposure over whole session
HM	During head movements before specific task
Task	During task performance
Cum	Cumulative exposure up to this task
SMF	Static Magnetic Field exposure
TVMF	Time-varying magnetic field exposure

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Chapter 4

Simultaneous exposure to MRI-related static and low-frequency movement-induced time-varying magnetic fields affects neurocognitive performance; a double-blind randomized crossover study

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ABSTRACT

This experimental study aims to separate neurocognitive effects resulting from exposure to static magnetic stray fields (SMF) alone and the combination of SMF and low- frequency movement-induced time-varying magnetic fields (TVMF) from a 7 Tesla (T) MRI scanner in stand-by mode. In a double-blind randomized crossover experiment, 36 healthy volunteers underwent four sessions, two exposed conditions and two corresponding sham conditions. The exposure conditions were in front of the scanner bore and consisted of 1.0 T SMF with or without 2.4 T/s TVMF, induced by standardized head movements before each of the five neurocognitive tasks. These specific tasks were selected because previous experiments showed negative effects of SMF+TVMF exposure on test performance. Exposure to SMF in combination with TVMF decreased verbal memory performance significantly and changed visual acuity. Similarly, attention and concentration were negatively affected with borderline significance. Exposure to SMF only did not have significant effects on performance on any of the tasks. Neurocognitive effects were only observed when simultaneously exposed to SMF and TVMF from a 7 T MRI scanner. Therefore, exposure to TVMF seems essential in eliciting the neurocognitive effects in our present and, presumably, previous experiments.

4.1 INTRODUCTION

Magnetic Resonance Imaging (MRI) is a popular diagnostic and research instrument, with more than 20,000 systems presently in use worldwide (Moser et al. 2012). Since the introduction of the first scanner in towards the end of the 1970s, advancing technology has allowed a more than 200-fold increase in magnetic field strength from the very first 0.04 Tesla (T) whole body scanner up to the newest systems of 11.7 T (Edelstein et al. 1981; Schaap et al. 2013). With this increase in magnetic field strength, workers and patients started reporting transient sensory symptoms. An exposure-response relation was found for symptoms such as metallic taste, nausea, and dizziness when in the vicinity of the scanner in stand-by mode (i.e., when exposed to static magnetic (stray) fields (SMF) (Schaap et al. 2014). Besides the reported complaints, more fundamental effects were observed in experimental studies. For example, exposure to the homogeneous SMF inside a 3 T or 7 T scanner bore induced involuntary eye movements (nystagmus) (Roberts et al. 2011), although no changes in neurocognitive function were observed at these field strengths inside the scanner (Heinrich et al. 2013; Lepsien et al. 2012). Induction of additional time-varying magnetic fields (TVMF) by moving a bed in and out of the bore did not change these effects. However, experiments performed in the inhomogeneous magnetic stray field outside a 7 T scanner bore showed short-lived acute effects on neurocognitive functions and postural stability. Decreased visual and motor performance (de Vocht et al. 2006), attention and concentration, spatial orientation (van Nierop et al. 2012), and postural body control were observed (van Nierop et al. 2013).

To unravel the origins of these neurocognitive effects, it is important to separate effects of different types of magnetic fields, because they point towards different mechanisms (Glover et al. 2007). As yet, it is still debated whether observed effects outside the bore are due to exposure to SMF alone or results from the combination of exposure to both SMF and TVMF. One of the proposed mechanisms is the interaction of SMF with the rotational sensors of the vestibular organ by Lorenz forces (Antunes et al. 2012; Glover et al. 2007; Roberts et al. 2011). However, whether stimulation of the vestibular system by SMF can account for changed neurocognitive performance is still unclear (Hanes et al. 2006). Another conceivable mechanism proposes that electrical currents are induced by TVMF (i.e., movement through the SMF, better known as Faraday's Law). In fact, these currents

can stimulate or inhibit neuron activity in the brain (Iles 2005). It is important to know which exposures affect neurocognitive functions, because this could have practical implications for employees and patients exposed. In particular, employees such as radiographers, anesthesiologist, and surgeons are exposed repeatedly and need to maintain a high level of precision and concentration. Moreover, with the quick development, implementation, and broadened range of applications of stronger MRI systems (Schaap et al. 2013) it is important to know which exposure should be controlled.

The aim of our study was to separately assess neurocognitive effects from exposure to SMF alone and those resulting from simultaneous exposure to SMF and movement-induced TVMF to gain more insight into the possible working mechanism(s) involved. To this end, we performed a double-blind randomized crossover experiment in which healthy subjects were exposed to four conditions: a combination of 1.0 T SMF and head movements inducing a 2.4 T/s TVMF, 1.0 T SMF only, and two corresponding sham conditions without SMF (i.e. with and without head movements).

4.2 METHODS

Subjects

A total of 36 healthy volunteers participated in the experiment (6 men and 30 women) with an average age of 22 ± SD 2.74 years (range between 18 and 30 years) recruited with flyers on bulletin boards at Utrecht University. Of the total group of responders who filled in a screening questionnaire (n=114), the first 36 eligible subjects were enrolled in the study based on the following exclusion criteria: pregnancy, self-reported presence of MRI-incompatible elements in the body, history of neurological disease, serious vision deficiencies, use of medication (except for birth control), soft or hard drugs, and excessive use of alcohol (>2 standard units per day) or coffee (>5 cups per day).

The majority of the study population (19 subjects) reported they had never seen an MRI scanner before. Thirteen subjects underwent an MRI scan once, two subjects had undergone a scan twice, one subject had undergone a scan three times, and one subject had undergone a scan five times. However, none of them had ever

worked with MRI or had been in a 7 T MRI room before. Subjects were asked to abstain from consuming alcohol and caffeine for 24 and 3 h, respectively, before the experiment. The study was approved by the local medical ethics research committee of the University Medical Center Utrecht.

Experimental design

A double-blind randomized crossover design was used in which each volunteer underwent a training session, followed by four experimental sessions with 1 h in between sessions over 2 consecutive days (Fig. 1). A single session covered five neurocognitive tasks and took on average 15 minutes and was conducted during the same time of the day for each individual subject.

There were two exposure sessions in the stray fields of a passively shielded 7.0 T Philips Achieva research system (University Medical Center Utrecht) wherein the subject sat on a fixed chair with their back toward the bore of the MRI magnet. In one session, subjects were exposed to 1.0 T SMF only (SMF), and in the other session they were exposed to a combination of 1.0 T SMF and 2.4 T/s TVMF (SMF+TVMF) as determined with a dosimeter placed on top of their head during the experiment (Magnetic Field Dosimeter, University of Queensland, Australia (Fuentes et al. 2008)). In line with our previous experiment (van Nierop et al. 2012), low-frequency TVMF were induced about 15 s before every single test by standardized head movements covering an angle of 180° in 0.8 s: 10 head movements in a vertical direction followed by 10 head movements in a horizontal direction. The start of each movement was indicated by an auditory cue.

There were also two corresponding unexposed sham sessions (<25 mT) in a standard room: one without (sham) and one with similar standardized head movements (sham+HM) before every single test. In the sessions without head movements (sham and SMF), subjects had a 5-s break before every test to have a similar total exposure duration compared with the sessions with head movements.

Before each session, subjects were checked for metallic components for safety reasons, and they were asked to complete a questionnaire about their current symptoms. A short questionnaire on side effects and perception of whether or not they had been exposed to magnetic fields was completed after each session by both the subject and the experimenter.

A) Setup of the experiment

B) Experimental session

Time	Task/ activity	Description of the task
	Head movement or break	
	RBMT immediate	Recall of a short story read by the test leader
	Head movement or break	
	Line Bisection	Mark the middle of 20 horizontal lines as fast as possible
	Head movement or break	
	Pursuit aiming Large + Small	Place dots in circles in 60 s
	Head movement or break	
	F.A.C.T. right eye	Recognize the direction of the lines with shrinking contrast with left eye blinded
	Head movement or break	
	F.A.C.T. left eye	Recognize the direction of the lines with shrinking contrast with right eye blinded
	Head movement or break	
	Simple reaction task	Press the target button when it alights (1 option) and return to the home button, 30 repeats
	Head movement or break	
	Complex reaction task	Press the target button when it alights (9 option) and return to the home button, 30 repeats
	Head movement or break	
	Inhibition reaction task	Press the target button left to the one that alights (8 option) and return to the home button, 30 repeats
	Head movement or break	
	RBMT recall	Recall the short story read by the test leader at the start of the session

Figure 1 Set-up of the experiment (A). Each subject underwent a training session followed by 4 experimental sessions in a randomized crossover design. An exposure and corresponding sham exposure session were always conducted on the same day. An experimental session took on average 15 minutes including 5 different neurocognitive tasks as specified (B).

Randomization and masking

The order of the four experimental sessions was randomly allocated by a computer, and balanced across all subjects where an exposure and corresponding sham condition were always assessed on the same day. Several measures were taken to ensure a double-blind experiment. To hide the exposure condition, i.e. whether they sat in front of the MRI scanner or in the sham room, subjects and experimenter were blind guided by the experiment coordinator (L.v.N.) into a standardized tent (210x140x90 cm). In addition, in the sham room a digital audio file playing the acoustic noise of an MRI system cryogen pump was used.

Test battery

Neurocognitive tests which revealed an effect of exposure to magnetic fields in at least one of the previous experiments (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; van Nierop et al. 2012) were selected in the current test battery (Fig. 1B). For safety reasons, all these tests were suitable for use in a strong magnetic field. The included tests were the Rivermead Behavioural Memory Test (RBMT) to assess (long term) verbal memory (Wilson et al. 1989), the line-bisection task to testspatial orientation (Schenkenberg et al. 1980), the pursuit aiming task to test eye-hand coordination (World Health 1986), the Functional Acuity Contrast Test (F.A.C.T.®) to determine visual acuity, and a reaction task with a simple, complex and inhibition part to assess attention and concentration (van Zomeren et al. 1987).

Data analysis

Statistical analyses of the effect of exposure on test performance were performed using linear mixed effects models in IBM SPSS version 20.0. Test performance was adjusted for practice effects (session number 1, 2, 3, or 4), sex (n=6/36 [17%] male and n=30/36 [83%] female) and sensitivity to motion sickness based on the motion sickness questionnaire (no sensitivity, n=10/36 [28%]; moderate sensitivity, n=22/36 [61%]; high sensitivity, n=4/36 [11%]) (Sup. Table S1). Subjects were included as random effects using heterogeneous compound symmetry that assumes similar correlation between residuals of the same subject but no correlation between different subjects.

For every test, the marginal mean test performance of all participants was estimated for each of the conditions as follows:

$$\text{Marginal mean} = \text{Intercept} + R.C._{\text{exposure condition}} + 0.25*(\sum R.C._{\text{Session1-4}}) + (0.17*R.C._{\text{male}}+0.83*R.C._{\text{female}}) + (0.28*R.C._{\text{not motion sick}}+ 0.61*R.C._{\text{moderate motion sick}} + 0.11*R.C._{\text{high motion sick}})$$

where R.C. is the regression coefficient of the model for the specific factor.

In addition, pairwise comparison of the exposure conditions with their respective sham conditions (SMF versus sham and SMF+TVMF versus sham+HM) were estimated. Statistical significance was defined as $P<0.05$. Data from most tasks were normally distributed. Only data from the F.A.C.T. task had to be log10 transformed prior to statistical analyses, because the relationship between the steps is not linear (Gilmore 2002).

4.3 RESULTS

All 36 subjects completed the four experimental sessions, resulting in 144 observations per task, which were included in the statistical analyses.

The mean test scores and standard deviations for all neurocognitive tasks in the four experimental conditions are presented in Table 1. The majority of the mean test scores in the unexposed condition with head movements (sham+HM) are comparable with those obtained in our previous experiment (van Nierop et al. 2012) (Sup. Table S2). Table 2 and Figures 2–6 show the estimated marginal group mean of test performances (and standard error) in the sham, sham+HM, SMF, and SMF+TVMF conditions resulting from the mixed model analysis and adjusted for session, sex, and reported motion sickness.

Comparison of test performance in the SMF and corresponding sham condition did not show significant changes in any of the cognitive tasks. Moreover, comparing test performance in the SMF+TVMF with the sham+HM condition showed statistically significant effects on the RBMT and F.A.C.T. More specifically, in the RBMT verbal memory task, a decreased test performance in the SMF+TVMF

was observed for the immediate recall (-7.8%, P=0.079), which was significant in the delayed recall (-11.3%, P=0.037).

Visual acuity as assessed by the F.A.C.T. did not indicate a consistent effect of (either SMF or) SMF+TVMF exposure, since SMF+TVMF exposure revealed an increased performance at 3.0 cycles per degree and a decreased performance at 6.0 cycles per degree (7.4%, P=0.058 and -12.5%, P=0.025, respectively).

With regard to the reaction task, motion time and disengagement time both showed a small nonsignificant increase when exposed to SMF+TVMF over all complexity levels of the task. This reached borderline statistical significance for disengagement time at the simple (4.3%, P=0.085) and at the complex reaction time task (4.4%, P=0.099).

No significant effects were found for spatial orientation on the line bisection task. In fact, subjects performed almost perfectly in bisecting lines at the exact center in the sham condition, whereas a bias of 1.6% to the left is normally found among healthy subjects (Bradshaw et al. 1985). When exposed to SMF, lines were slightly more bisected toward the left, and this nonsignificant effect became more pronounced in both the sham+HM and SMF+TVMF conditions. Finally, no significant effects of either SMF or SMF+TVMF exposure were found on the speed and precision performance on both levels of the pursuit aiming task. Neither head movement nor SMF nor the combination of SMF+TVMF exposure seemed to influence speed or precision of test performance when compared with sham on both levels of the pursuit aiming task.

Table 1 Average test performance, standard deviations (SD) and geometric means (GM) for each neurocognitive test in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and static magnetic field conditions with time-varying magnetic fields induced by head movements (SMF+TVMF) (N=36)

		sham			SMF			sham+HM			SMF+TVMF		
Task	**Measure**	**Mean**	**SD**	**GM**	**Mean**	**SD**	**GM**	**Mean**	**SD**	**GM**	**Mean**	**SD**	**GM**
RBMT[a]	Immediate	11.5	3.8	10.8	11.7	3.4	11.2	12.1	3.6	11.5	11.0	4.2	10.2
	Recall	9.8	4.3	8.7	10.5	3.4	9.8	10.7	3.4	10.1	9.3	4.6	7.8
	Difference	83.1	18.1	80.2	89.3	13.9	88.2	89.0	14.6	87.7	81.7	22.8	72.3
Line Bisection[b]	Deviation	101.9	6.7	101.7	101.6	7.3	101.4	101.6	7.0	101.3	101.3	7.2	101.0
Pursuit[c]	Speed	140.6	15.3	139.9	139.1	17.3	138.1	140.8	15.2	140.0	139.7	14.5	139.0
Small	Precision	79.2	9.5	78.6	79.1	9.8	78.5	78.3	9.6	77.7	79.3	8.7	78.8
Large	Speed	147.6	13.9	147.0	145.6	15.8	144.8	147.7	15.2	147.0	148.0	14.5	147.3
	Precision	92.0	4.2	92.0	91.9	4.7	91.7	92.1	5.0	92.0	92.4	4.4	92.3
F.A.C.T.[d]	1.5 cpd.	297.5	53.4	291.4	295.3	51.6	289.3	299.7	41.2	296.6	299.8	43.2	296.1
	3.0 cpd.	418.3	108.5	402.4	406.7	101.2	393.3	413.3	103.4	399.1	430.9	104.4	416.9
	6.0 cpd.	333.6	130.8	306.5	337.5	128.2	308.2	344.4	121.9	323.3	309.2	131.6	281.6
	12.0 cpd.	126.6	71.4	106.1	133.2	90.0	104.3	113.6	73.1	92.1	106.8	63.4	83.0
	18.0 cpd.	39.5	33.8	0.0	30.0	26.4	20.2	31.1	27.2	0.0	41.1	46.1	24.2
Simple RT[e]	Reaction time	329.1	38.9	327.0	329.1	37.2	327.2	333.2	37.3	331.2	329.5	36.0	337.6
	Motion time	224.8	59.3	218.1	226.6	63.5	218.1	223.2	58.1	217.0	225.0	55.2	218.7
	Disengagement	132.8	27.4	130.1	131.5	28.6	128.3	129.7	34.4	125.3	135.0	34.3	130.7
Complex RT	Reaction time	397.3	41.3	395.3	393.7	32.8	392.4	390.0	45.8	387.5	389.4	33.0	388.0
	Motion time	255.3	61.7	248.6	245.4	58.7	238.8	246.6	58.8	240.4	250.7	63.7	243.3
	Disengagement	131.7	27.0	128.9	129.0	26.4	126.1	128.2	31.8	124.2	134.7	33.2	131.1
Inhibition RT	Reaction time	426.0	41.5	424.1	427.1	46.7	424.7	424.9	44.4	422.7	424.6	41.2	422.6
	Motion time	261.9	64.0	254.9	253.4	66.5	245.2	257.4	67.9	249.1	256.5	63.5	249.0
	Disengagement	130.6	25.3	128.0	134.6	27.5	131.6	131.1	27.8	128.0	133.8	28.9	130.6

All data represents raw untransformed data. [a]Recall of a short story read by the test leader, given in correct words and the Difference in %. [b]Mark the middle of 20 horizontal lines, center of the line is defined as 100.0. [c]Place dots in small circles in 60 seconds, Speed: Total marked items, Precision: % correct items of total marked items. [d]Recognizing the direction of lines with shrinking contrast and cycle frequencies, for different cycles per degree (cpd). [e]RT reaction task (in milliseconds); Press the target button when alights and return to the home button with different levels; one button option (simple task), 9 button options (complex task) press button left of the button that lights up (inhibition). Reaction time: time to release home button after alight of target button. Motion time: time needed to go from home button to target button. Disengagement time: time needed to release the target button.

Table 2 Estimated marginal means of test performance in the sham condition, SMF condition, sham condition with head movements (Sham+HM), and TVMF condition within the SMF (SMF+TVMF) using a mixed effects model (N=36)

					95% CI		
			Estimate	St. Error	Lower	Upper	p-value
RBMT	**Immediate**	sham	11.50	0.56	10.38	12.63	
		SMF	11.75	0.56	10.62	12.87	0.647
		sham+ HM	12.00	0.56	10.87	13.12	
		SMF+ TVMF	11.06	0.56	9.93	12.18	0.079
	Delayed	sham	9.80	0.59	8.62	10.97	
		SMF	10.56	0.59	9.38	11.74	0.178
		sham+ HM	10.56	0.59	9.38	11.73	
		SMF+ TVMF	9.37	0.59	8.19	10.54	**0.037**
	Difference	sham	-1.66	0.29	-2.24	-1.08	
		SMF	-1.20	0.29	-1.77	-0.62	0.251
		sham+ HM	-1.40	0.29	-1.97	-0.82	
		SMF+ TVMF	-1.78	0.29	-2.36	-1.20	0.338
Line Bisection[a]		sham	100.11	0.30	99.51	100.70	
		SMF	99.82	0.31	99.22	100.41	0.376
		sham+ HM	99.73	0.31	99.13	100.33	
		SMF+ TVMF	99.44	0.30	98.85	100.04	0.387
Pursuit aiming Small circles	**Speed**	sham	140.64	2.59	135.41	145.88	
		SMF	138.98	2.59	133.74	144.21	0.255
		sham+ HM	140.62	2.59	135.39	145.86	
		SMF+ TVMF	139.98	2.59	134.75	145.21	0.659
	Precision	sham	79.16	1.55	76.04	82.27	
		SMF	79.09	1.55	75.97	82.21	0.951
		sham+ HM	78.42	1.55	75.30	81.54	
		SMF+ TVMF	79.25	1.55	76.13	82.37	0.429
Pursuit aiming Large circles	**Speed**	sham	147.65	2.42	142.77	152.54	
		SMF	145.58	2.42	140.70	150.47	0.134
		sham+ HM	147.62	2.42	142.73	152.50	
		SMF+ TVMF	148.04	2.42	143.16	152.93	0.757
	Precision	sham	91.86	0.73	90.40	93.33	
		SMF	92.21	0.73	90.75	93.68	0.584
		sham+ HM	92.10	0.73	90.63	93.56	
		SMF+ TVMF	92.29	0.73	90.82	93.75	0.767
F.A.C.T.	**1.5 cpd.**	sham	292.42	1.03	275.17	310.30	
		SMF	292.42	1.03	275.20	310.39	0.994
		sham+ HM	299.23	1.03	281.94	317.95	
		SMF+ TVMF	297.85	1.03	280.29	316.05	0.817
	3.0 cpd.	sham	405.51	1.05	370.06	443.63	
		SMF	390.84	1.05	356.94	427.86	0.323
		sham+ HM	394.46	1.05	360.57	432.25	
		SMF+ TVMF	423.64	1.05	386.73	463.72	0.058
	6.0 cpd.	sham	308.32	1.07	268.81	353.96	
		SMF	311.89	1.07	271.89	358.08	0.845
		sham+ HM	320.63	1.07	279.10	367.52	
		SMF+ TVMF	280.54	1.07	244.21	321.59	**0.025**

Table 2 continued

	12.0 cpd.	sham	106.91	1.12	84.93	134.70	
		SMF	102.80	1.12	81.56	129.33	0.664
		sham+ HM	94.84	1.12	75.35	119.52	
		SMF+ TVMF	86.30	1.12	68.43	108.63	0.309
	18.0 cpd.	sham	27.35	1.18	19.69	37.98	
		SMF	21.83	1.18	15.70	30.32	0.115
		sham+ HM	23.39	1.18	16.84	32.48	
		SMF+ TVMF	25.29	1.18	18.22	35.14	0.578
Simple RT	**RT**	sham	329.48	5.96	317.43	341.52	
		SMF	327.98	5.96	315.94	340.03	0.675
		sham+ HM	333.39	5.96	321.35	345.43	
		SMF+ TVMF	329.40	5.94	317.39	341.41	0.260
	MT	sham	224.04	9.99	203.92	244.16	
		SMF	228.14	9.99	208.01	248.26	0.327
		sham+ HM	222.39	9.99	202.27	242.51	
		SMF+ TVMF	225.14	9.98	205.05	245.23	0.506
	DT	sham	132.41	5.11	122.12	142.70	
		SMF	131.52	5.11	121.22	141.81	0.781
		sham+ HM	129.45	5.11	119.16	139.74	
		SMF+ TVMF	134.99	5.09	124.73	145.25	0.085
Complex RT	**RT**	sham	396.07	6.39	383.23	408.91	
		SMF	393.92	6.40	381.07	406.76	0.620
		sham+ HM	390.96	6.39	378.12	403.80	
		SMF+ TVMF	389.14	6.37	376.34	401.93	0.671
	MT	sham	254.12	10.18	233.63	274.61	
		SMF	247.50	10.18	227.01	267.99	0.104
		sham+ HM	246.22	10.18	225.73	266.71	
		SMF+ TVMF	250.36	10.17	229.90	270.83	0.303
	DT	sham	131.67	5.00	121.58	141.76	
		SMF	128.42	5.00	118.33	138.51	0.350
		sham+ HM	128.77	5.00	118.68	138.86	
		SMF+ TVMF	134.49	4.98	124.44	144.54	0.099
Inhibition RT	**RT**	sham	424.09	7.34	409.31	438.86	
		SMF	426.85	7.34	412.08	441.63	0.554
		sham+ HM	425.65	7.34	410.87	440.42	
		SMF+ TVMF	424.65	7.32	409.92	439.39	0.831
	MT	sham	259.85	11.17	237.05	282.66	
		SMF	255.74	11.17	232.93	278.54	0.331
		sham+ HM	257.05	11.17	234.25	279.85	
		SMF+ TVMF	256.66	11.16	233.88	279.43	0.925
	DT	sham	129.89	4.56	120.71	139.07	
		SMF	133.95	4.56	124.77	143.13	0.159
		sham+ HM	131.84	4.56	122.65	141.01	
		SMF+ TVMF	133.61	4.55	124.46	142.77	0.534

Cycles per degree (Cpd) reaction time task (RT) in milliseconds, reaction time (RT) motion time (MT) disengagement time (DT) confidence interval (CI)

Test performances were adjusted for practice effects, sex and sensitivity to motion sickness

[a] P-values are presented of pairwise comparison between sham versus SMF and sham+HM versus SMF+TVMF

[b] Model was additionally adjusted for hand preference

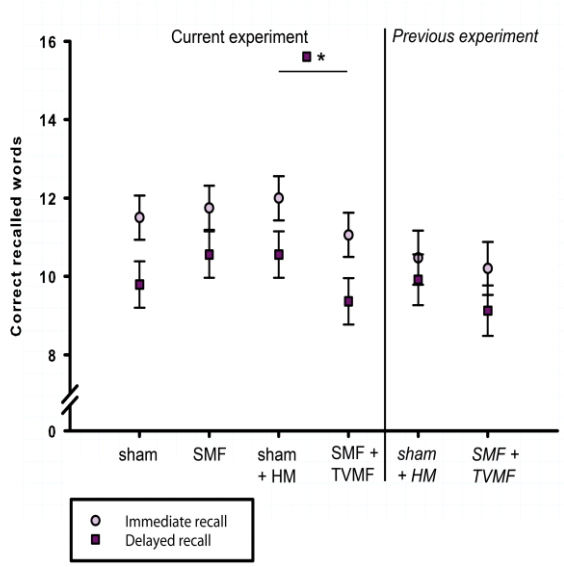

Figure 2 Estimated test performance on the RBMT with correspond ding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+ TVMF) in current (N=36) and previous experiment (N=30). *P<0.05

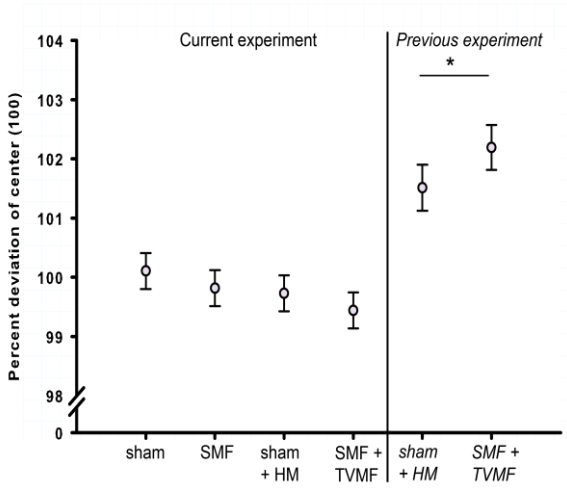

Figure 3 Estimated test performance on the line bisection task with corresponding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF) in current (N=36) and previous experiment (N=30). *P<0.05.

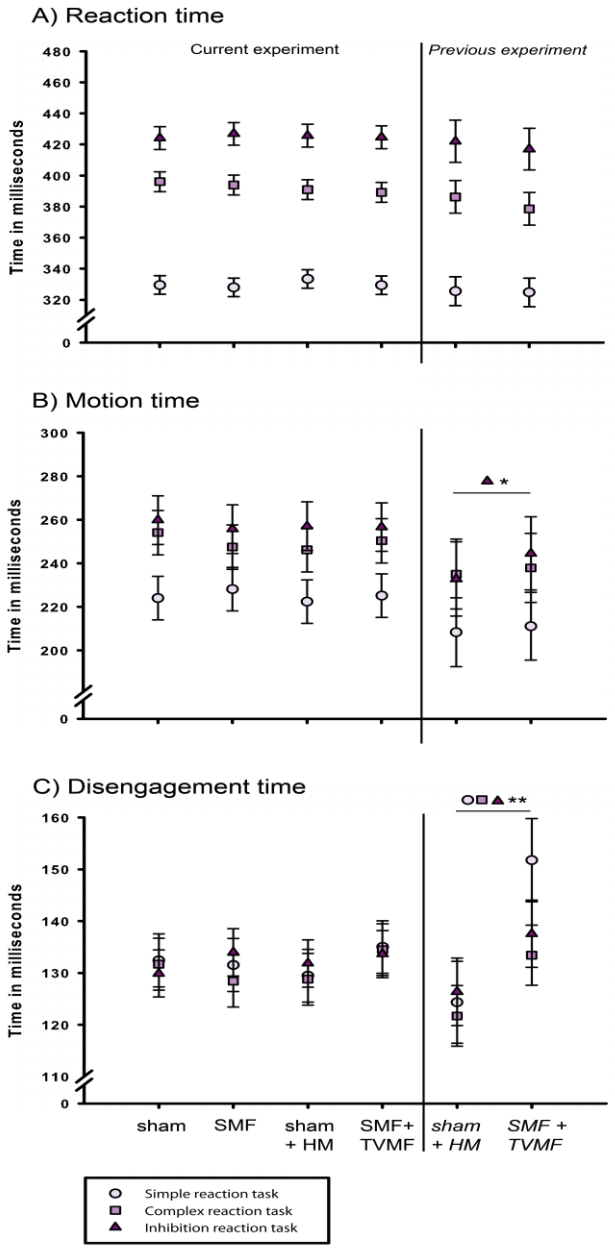

Figure 4 Estimated test performance on the reaction task reaction time (A), motion time (B) and disengagement time (C) with corresponding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF) in current (N=36) and previous experiment (N=30). *P<0.05; **P<0.001.

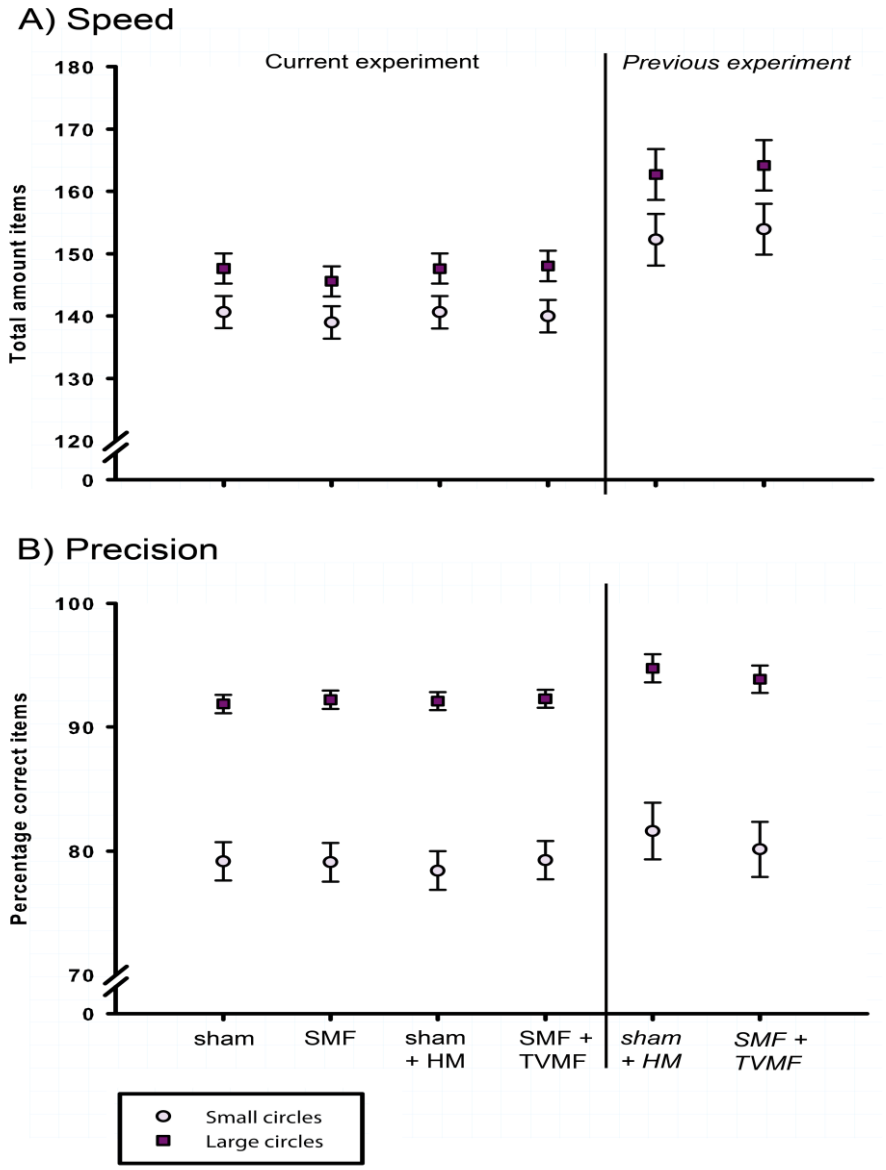

Figure 5 Estimated test performance on the pursuit aiming task speed (A) and precision (B) with corresponding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF) in current (N=36) and previous experiment (N=30).

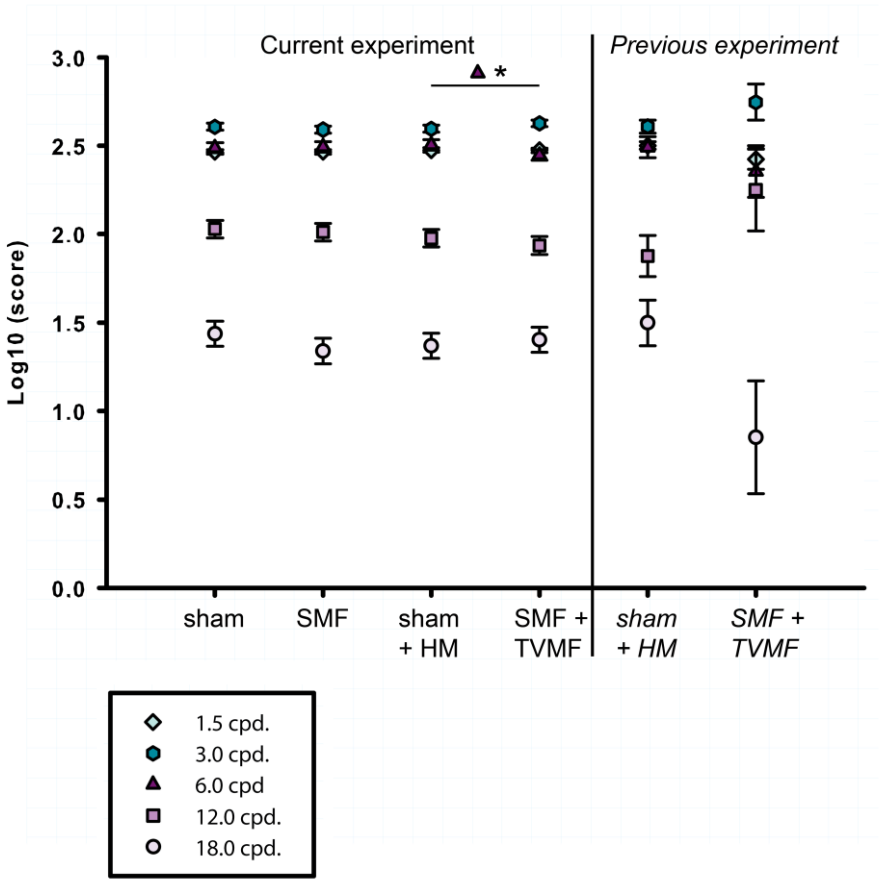

Figure 6 Estimated test performance on the F.A.C.T. with corresponding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF) in current (N=36) and previous experiment (N=30). *P<0.05.

4.4 DISCUSSION

Our experiment showed that not SMF exposure by itself, but simultaneous exposure to SMF and low-frequency head movement-induced TVMF from a 7 T MRI scanner affected performance significantly for two of the five neurocognitive tasks compared with a sham condition with head movements. In particular, verbal memory was reduced as indicated by immediate recall and delayed recall in the RBMT. Visual acuity was reduced at 6.0 cycles per degree as assessed by the F.A.C.T. and increased at 3.0 cycles per degree. In addition, borderline significance was reached for attention and concentration based on the reaction time task, whereas disengagement time was increased in the simple and complex reaction time task. In contrast, spatial orientation and visuomotor performance as assessed by the line bisection and pursuit aiming task were not affected by either exposure to SMF or in combination with TVMF.

The decrease in performances of RBMT, F.A.C.T., and reaction time task concerns only subtle changes that cannot be placed within one focalized neurocognitive domain. Nevertheless, such changes might possibly hamper performance, especially when accurate professional functioning (e.g., during medical procedures) is at stake. The RBMT reflects an everyday life situation: recalling a short newspaper article upon hearing it once. Fewer items were recalled correctly when exposed to the combination of SMF and TVMF. This everyday life situation also applies to the reaction task in which attention is divided over multiple aspects simultaneously. Disengagement time in the reaction task is defined as the ability to disengage from a trial in order to prepare for the next trial. In both tasks, performance is strongly dependent on the integration of attention, concentration, speed of processing, and working memory capacity (Ganor-Stern et al. 1998; Lezak 2002). Therefore, our current and previous findings (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; van Nierop et al. 2012) point predominantly toward specific aspects of attention, concentration, and altered working memory that can result in a decreased retrieval of declarative memory and an increased disengagement time for the reaction task. In accordance, no significant effect of exposure to SMF alone or in combination with TVMF was found for tasks that required less mental effort (e.g., pursuit aiming and line bisection).

Performance on the F.A.C.T. did not show a consistent and uniform change in visual acuity, which makes the significant results questionable. Although the

results of the immediate and delayed recall (RBMT) and disengagement time (reaction task) are comparable to the results obtained in our previous experiment (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; van Nierop et al. 2012), the effects on other tasks appeared to be less pronounced or even in the opposite direction.

Both exposure conditions and head movements can induce a change in test performance. For example, during head movement, the vestibular and visual system receives sensory input that can either distract and decrease test performance or arouse and increase test performance. Exposure to SMF can induce Lorentz forces within the endolymph fluid of the semicircular canals, which can change the firing rate of the cupula (Antunes et al. 2012; Roberts et al. 2011). From here, neuronal afferents transmit the signal to other brain areas, which can result in changed test performance on various tasks (see Utz et al. 2010 for a review). Exposure to TVMF can result in electromagnetic induction, which can inhibit or facilitate neuron communication directly (Iles 2005; Silva et al. 2008). Exposure to SMF —and, more importantly, exposure to SMF+TVMF— could also result in a conflict between registered information by the visual and vestibular system (i.e., sensory conflict theory (Reason et al. 1975)). This might in turn affect cognitive test performance directly or indirectly via side effects such as nausea. Moreover, performance on each neurocognitive task requires the activation of different cortical areas and circuitries, arguing that not necessarily one of the three aforementioned mechanisms is exclusively involved or determinative for task performance. Although electromagnetic induction seems most conceivable for raising the cognitive effects as found is this research, additional effects of Lorenz forces or sensory conflicting information cannot be ruled out.

The experimental design was kept as similar as possible to that of our previous study (a double-blind randomized crossover design with similar exposure levels for SMF (1.0 T) and TVMF (2.4 T/s)). These exposures are within the limits of the ICNIRP guidelines (ICNIRP 2014), which are set at 2.0 T for SMF to prevent vertigo and 2.7 T/s for movement-induced TVMF to prevent peripheral nerve stimulation. Our selected subjects had similar characteristics with regard to age, education, and sex. However, a few differences were present. First, contrary to the previous experiment, volunteers were not excluded based on their self-reported vulnerability to motion sickness (Supplemental material Table S1). This could have resulted in larger between-subject variability in test performance as shown by the

larger standard deviations (Supplemental material Table S2) and consequently in fewer statistical significant results. Second, in the current test design, subjects were tested two times on two consecutive days compared with previous experiments in which subjects had three sessions with 1 week in between. Furthermore, volunteers were exposed for a shorter time in the current experiment compared with the previous experiment (15 versus 47 minutes) as a consequence of the much shorter test battery. This resulted in fewer series of head movements (eight versus 19, respectively) (Supplemental material Table S3). Finally, the test battery duration in the previous experiment was longer, which could have led to decreased concentration, possibly enhanced by effects of exposure to the TVMF. However, given the considerable differences in experimental design and findings, replication of our latest results is needed.

A strength of this study is the balanced, double-blind, randomized crossover design in which subjects served as their own controls. A double-blind experimental setup was created by using similar tents, blind guiding of subjects and the test leader into the tents, and use of MRI audio recordings in the sham condition. Subjects were not informed about the number and order of sham and exposure sessions. Based on a questionnaire at the end of each session, perception of 'exposure' or 'no exposure' was correct in 63% and 53% of the sessions by participants and the test leader, respectively.

In conclusion, the results of this study suggest that the subtle decreased performance for verbal memory and the non-significant decreased attention and concentration are more likely attributable to simultaneous exposure to SMF and movement-induced TVMF rather than SMF alone.

ACKNOWLEDGEMENTS

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SUPPLEMENTAL MATERIAL

Table S1 Score on the short version of the motion sickness questionnaire (Golding 1998) and classification for the subject population in previous experiment (van Nierop et al. 2012) (N=30) and current experiment (N=36)

Classification of sensitivity	MSSQ score	Previous experiment # Subjects	Current experiment # Subjects
Low	3	15	10
Medium	4	5	7
	5	9	10
	6	1	5
high	7	0	2
	8	0	1
	9	0	1

Sensitivity to motion sickness was defined as a sum score for three types of symptoms in last 10 years (general sensitivity, nausea and puking) on a four-point Likert scale ranging from one (not at all) to four (very often). Total MSSQ score between 3 and 12 points.
Classification of low, medium and high sensitivity to motion sickness as adjusted for in mixed model

Table S2 Average test performance, standard deviations (SD) for each neurocognitive test, in the sham condition with additional head movements (sham+HM), in the current and previous experiment. The total group and a subgroup restricted to subjects with MSSQ score <7 is separately shown.

		Current exp. sham+HM MSSQ<10 N=36		**Current exp. sham+HM MSSQ<7 N= 32**		**Previous exp. sham+HM MSSQ<7 N=30**	
Task	**Measure**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
RBMT	immediate	**12.1**	3.6	**11.8**	3.7	10.1	3.4
	recall	**10.7**	3.4	10.3	3.4	9.5	3.3
	Difference %	89.0	14.6	88.3	15.1	93.5	16.6
Line Bisection	Deviation in %	**101.6**	7.0	101.5	7.2	100.3	6.7
Pursuit L	Speed	147.7	15.2	148.5	15.8	156.3	15.9
	Precision %	92.1	5.0	92.6	4.2	94.1	3.2
Pursuit S	Speed	140.8	15.2	140.8	16.0	148.0	13.9
	Precision %	78.3	9.6	79.1	9.7	81.5	7.3
F.A.C.T.	1.5 cpd.	299.7	41.2	302.2	41.2	303.3	42.8
	3.0 cpd.	413.3	103.4	422.0	96.9	400.5	98.6
	6.0 cpd.	344.4	121.9	**354.5**	121.5	316.5	125.9
	12.0 cpd.	113.6	73.1	**119.1**	73.4	101.8	68.6
	18.0 cpd.	31.1	27.2	30.9	24.9	29.4	14.8
RTT (simple)	Reaction time	333.2	37.3	330.0	37.0	330.7	40.8
	Motion time	223.2	58.1	225.3	61.1	217.1	54.4
	Disengagement	**129.7**	34.4	127.3	35.3	116.4	36.1
RTT (complex)	Reaction time	390.0	45.8	387.1	43.8	395.3	44.8
	Motion time	246.6	58.8	245.7	62.0	240.0	58.1
	Disengagement	128.2	31.8	126.3	32.5	124.5	20.5
RTT (inhibition)	Reaction time	424.9	44.4	420.5	40.2	442.6	55.5
	Motion time	257.4	67.9	257.7	71.2	240.7	56.2
	Disengagement	131.1	27.8	128.9	28.7	124.9	27.2

Bold values; more as 10% higher or lower than mean score in previous experiment (van Nierop et al. 2012)

Table S3 Time in minutes of neurocognitive tasks and number of sets of standardized head movement (HM) up to the task in previous (van Nierop et al. 2012) and current experiment

Previous Experiment		
Time	**Task**	**HM**
1	RBMT immediate	1
18	Line Bisection	7
29	Pursuit Aiming	11
32	F.A.C.T. (2x)	12-13
40	RBMT delayed	15
44-47	Reaction task (3x)	17-18-19

Current Experiment		
Time	**Task**	**HM**
1	RBMT immediate	1
3	Line Bisection	2
5	Pursuit	3
7	F.A.C.T. (2x)	4-5
12-15	Reaction task (3x)	6-7-8
33	RBMT delayed	15

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Chapter 5

MRI-related static magnetic stray fields and postural body sway: a double-blind randomized crossover study

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ABSTRACT

We assessed postural body sway performance after exposure to movement induced time-varying magnetic fields in the static magnetic stray field in front of a 7 Tesla (T) magnetic resonance imaging scanner. Using a double blind randomized crossover design, 30 healthy volunteers performed two balance tasks (i.e., standing with eyes closed and feet in parallel and then in tandem position) after standardized head movements in a sham, low exposure (on average 0.24 T static magnetic stray field and 0.49 $T \cdot s^{-1}$ time-varying magnetic field) and high exposure condition (0.37 T and 0.70 $T \cdot s^{-1}$). Personal exposure to static magnetic stray fields and time-varying magnetic fields was measured with a personal dosimeter. Postural body sway was expressed in sway path, area, and velocity. Mixed-effects model regression analysis showed that postural body sway in the parallel task was negatively affected ($p<0.05$) by exposure on all three measures. The tandem task revealed the same trend, but did not reach statistical significance. Further studies are needed to investigate the possibility of independent or synergetic effects of static magnetic stray field and time-varying magnetic field exposure. In addition, practical safety implications of these findings, e.g., for surgeons and others working near magnetic resonance imaging scanners need to be investigated.

5.1 INTRODUCTION

In the last 30 years, magnetic resonance imaging (MRI) has become an important diagnostic modality within clinical settings because of its broad range of applications and noninvasive advantages compared to other diagnostic methods like X-ray, PET, and CT. These advances have been enabled by the introduction of stronger magnetic field (MF) strengths of the machines up till the recently clinical available 14 Tesla (T) systems (Duyn 2012). These ultrahigh-field scanners are never switched off since changing the MF strength of the machine is a very time demanding and expensive procedure. Therefore, the static magnetic field (SMF) is always present, which necessitates strict safety rules about ferromagnetic materials that can become projectiles in the MRI room (de Vocht et al. 2006b; Klucznik et al. 1993; Schenck 2005). In addition, exposure of patients and personnel to these increasingly strong MFs raises concerns regarding their well-being and health.

Employees working near MRI-systems and patients exposed to MRI-related magnetic stray fields have been previously shown to report (transient) symptoms such as dizziness, vertigo, nausea, and metallic taste (de Vocht et al. 2006b; Schenck 1992; Wilen et al. 2011). Besides these reported sensory symptoms there is also experimental evidence for acute effects of exposure to strong MRI-related MFs on several neurocognitive functions like visual (spatial) perception, attention, and concentration (de Vocht et al. 2007; de Vocht et al. 2006a; de Vocht et al. 2003; van Nierop et al. 2012).

Given the above, exposure to MRI-related MFs could lead to acute symptoms and cognitive disturbances in professionals working near MRI systems. This is especially important when high levels of precision and performance are required, e.g., surgeons performing MRI-guided operations (Henk et al. 2005; Lewin et al. 2000; Liu et al. 2000; Razavi et al. 2003). Most surgeons and personnel stand upright during (part of) their work in the MRI room. Hence, it is of special interest to investigate whether standing balance in terms of postural sway is affected by exposure to a static magnetic stray field (SMF) and whether or not in combination with movement induced time-varying magnetic fields (TVMFs) of an MRI magnet.

In a double-blind randomized crossover study, we aimed to characterize acute effects of movement-induced TVMFs within the SMF around a 7.0 T MRI-magnet on postural body sway.

5.2 METHODS

Subjects

Healthy volunteers were recruited by flyers and advertisements on bulletin boards at Utrecht University. Exclusion criteria were: self-reported presence of MRI incompatible elements in the body, medical history pointing to a possible neurological or neuro-otological disease, serious vision deficiencies, use of medication (except for birth control pills), use of soft or hard drugs, excessive alcohol (>2 glasses per day), or coffee (>5 cups per day) consumption and sensitivity to motion sickness in adulthood.

Sensitivity to motion sickness in adulthood was defined as a score higher than 2 on a four-point rating scale (Likert scale) ranging from 1 (not at all) to 4 (very often) on at least one of three types of motion sickness symptoms, i.e., car sickness, see sickness, and air sickness. These questions were derived from the revised Motion Sickness Susceptibility Questionnaire (Golding 1998). Subjects reporting mild sensitivity to motion sickness in adulthood (i.e., scores <3) were included. This factor was taken into account in the analysis (see data analysis).

Thirty healthy volunteers who signed an informed consent participated in the experiment. Of all volunteers, nine were male and 21 were female with an average age of 23.8 (SD 6.5) years. All participants were asked to abstain from consumption of alcohol and caffeine (24 and 6 h resp.) prior to the start of the experiment since these can substantially affect standing balance (Franks et al. 1975). A modest incentive gift voucher was provided for every completed test session. The study was approved by the local medical ethics committee of the University Medical Center Utrecht, the Netherlands.

Experimental design

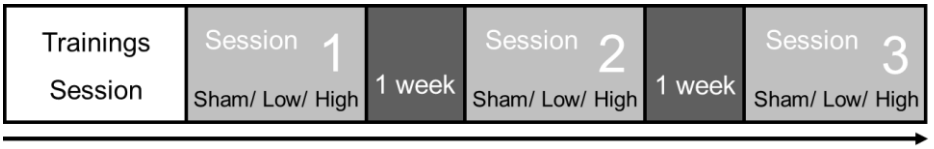
A double-blind randomized crossover design was used to examine postural body sway when in a sham, low and high SMF of a passively shielded 7.0 T MRI system (Philips Achieva research system located at University Medical Center Utrecht in the Netherlands).

The sequence of the three exposure conditions was balanced and assigned prior to the start of the experiment using a randomization protocol. Each subject was tested on three occasions conducted at the same time of day ±52 min (SD 48), with 1 week between each session (see Fig. 1a). A single session took on average 6 min in which two different balance tasks were assessed in standing position with eyes closed (see Fig. 1b). To reduce a possible practice effect on test performance, the subjects practiced both tasks once in a training session and also in every single experimental session right before the recorded task (Black et al. 1982).

In the low and high exposure conditions, subjects were tested in front of the MRI bore at two designated distances (see Fig. 2). Average SMF exposures were 0.24 and 0.37 T in the low and high exposure conditions, respectively. Immediately before each task TVMFs were induced by standardized head movements of on average 0.49 and 0.70 $T \cdot s^{-1}$ in the low and high exposure conditions, respectively. The head movements took about 16 s and consisted of 10 movements in the vertical and 10 in the horizontal direction between two visual markers (covering an angle of 180 degrees in 0.8 s). The start of each head movement was indicated by an auditory cue.

Prior to the balance task subjects sat for an hour on a chair with fixed position in a corresponding low (0.5 T) or high (1.0 T) exposure condition and performed several neurocognitive tasks reported elsewhere (van Nierop et al. 2012). Each of these neurocognitive tasks was preceded by the same standardized head movements, which in this case induced TVMFs of 1.2 and 2.4 $T \cdot s^{-1}$.

A) Setup of the experiment



B) Specifications of the experimental session

Time in min:sec	Activity
0:00	Practice parallel task
1:00	Head movements
1:16	Parallel task
1:46	Break
4:00	Practice tandem task
5:00	Head movements
5:16	Tandem task
5:46	End of experiment

Figure 1 Setup of the experiment (A) and specifications of the experimental session (B).
A) Each subject first underwent a training session followed by the first experimental session out of three. The experimental sessions were at the same time of the day with one week in between. Sham, low and high exposure conditions were randomized and balanced over the subjects. B) Setup of the time scheme for a single experimental session. After practicing the balance task with feet in parallel position, standardized head movements were made (in about 16 seconds ten movements in vertical and ten in horizontal directions), immediately followed by the recorded parallel task (30 seconds). After a small break of two minutes the same procedure was followed for the task with feet in tandem position. One experimental session took around 6 minutes to complete.

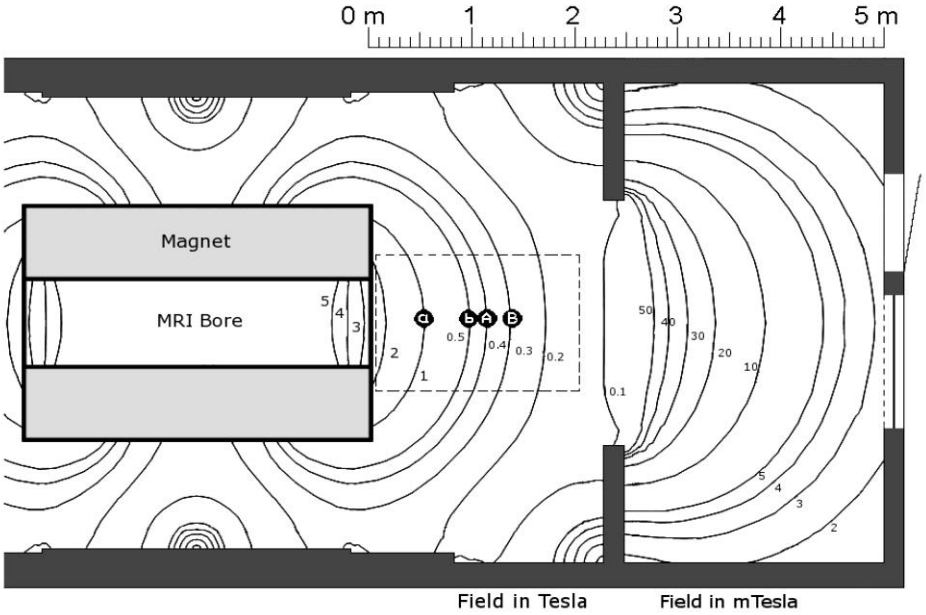


Figure 2 Top view map of the 7 T MRI with calculated field lines of the SMF as provided by Magnex Scientific Inc. Dots represent the positions of the subject in the exposure conditions within the tent (interrupted line). Circle A in front of the bore represents the test position (on average 0.37 T) after staying an hour in the high exposure position of 1.0 T (circle a). Circle B represents the test position (on average 0.24 T) after staying an hour in the low exposure position of 0.5 T (circle b). The tent was shifted when subject was in the low exposure position B/b. Distance to the bore in test position was around 90 (A) and 130 (B) centimeter. The sham condition was in a room opposite to the scanner room.

Exposure Assessment

Personal exposure to MFs was registered in real-time by use of a dosimeter (Magnetic Field Dosimeter, University of Queensland, Australia (Fuentes et al. 2008)) which was attached to the inside of a plastic helmet worn by the subject. The dosimeter registered exposure to SMF and TVMF in three directions, where

total static field $\|B\| = \sqrt{B_x^{\,2} + B_y^{\,2} + B_z^{\,2}}$ and

total time-varying field $\|dB/dt\| = \sqrt{(dB_x/dt)^2 + (dB_y/dt)^2 + (dB_z/dt)^2}$

Average exposure to the SMF and TVMF during head movements before each balance task was used as an estimate of exposure in the main analysis.

Blinding

Several measures were taken to develop a double blind setup: subjects were tested inside a standardized tent (210 x 140 x 190 cm^3) to hide the exposure condition. The subject and trained experimenter were blindly guided into and out of one of the tents by the experiment coordinator (LEvN). In addition, in the sham condition an audiotape played the acoustic noise of an MRI system in stand-by mode. Eight subjects reported to have undergone an MRI but none of the subjects or experimenters had ever worked with MRI or had seen the test room before. Prior to each session, subjects were checked for metallic components and after each session a questionnaire on perception of the actual exposure condition was completed.

Assessment of Postural Sway

For measuring postural sway a balance task was selected which could be safely used in an MRI environment. The balance task, better known as the Romberg test (Romberg 1853), had two levels of difficulty: the simple test, in which postural body sway was measured with feet next to each other in parallel position (0 cm apart), and an advanced test, with feet in tandem position, heel to toe (0 cm apart). Subjects had to stand upright barefoot with their arms alongside their body. After performing the standardized head movements, postural body sway with closed eyes was recorded real-time during 30 s by use of a balance belt around the waist, containing a shielded

2D accelerometer from Sensabalance Therapy Cushion 1.0 (Sensamove, Utrecht). The recording frequency of the device was 100 Hz.

Three sway endpoints were derived from the data record: postural sway path, sway velocity, and sway area (see Table 2 and Fig. 3). Sway path was defined as the total length of the swayed path in centimeter. Sway velocity was calculated as the average speed of movement over the sway path length in centimeter per second (mm/s). The correlation of this metric with sway path length will therefore be rather high. Sway area was defined as the total area within the outer bounds of a subject's sway path expressed in centimeter squared (mm^2). Higher test scores indicated poorer postural sway performance.

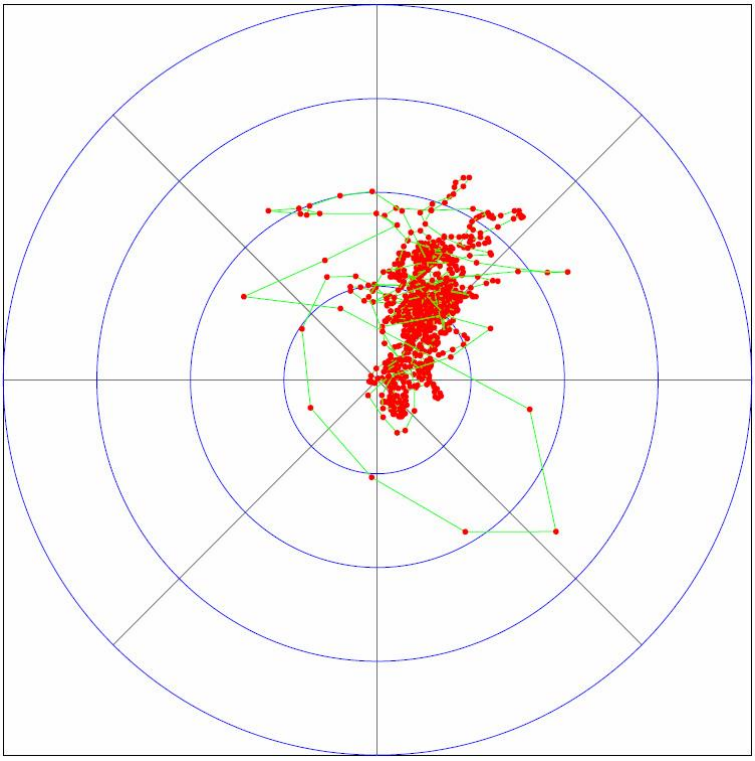


Figure 3 Example of a postural sway recording of a subject in the high exposure condition as viewed from above. Subject stood with feet in tandem position (heel to toe) with eyes closed. Measurement started after the head movements were completed, in the centre of the web and postural position was sampled at 100 Hz (represented by the dots) during 30 seconds. Sway path (in mm), area (in mm^2) and velocity (in mm/s) were computed as outcome measures. In this case, the depicted subject had a sway path of 31 mm, sway area of 494 mm^2 and sway velocity of 47 mm/s.

Data Analysis

Statistical analyses of interindividual and intraindividual differences in test performance in association with exposure were performed using mixed-effects models (Laird et al. 1982) in Statistical Package for Social Science version 16.0 (SPSS Inc., Chicago, IL). Four exposure metrics were entered as continuous variables in separate models assuming a log-linear exposure-effect association: (a) SMF exposure and (b) TVMF exposure, both measured during head movements before the parallel task; (c) SMF exposure and (d) TVMF exposure, both measured during head movements before the tandem task. Before modeling postural sway, endpoints were log(10)-transformed to improve the fit of the statistical models. All analyses were adjusted for order of the sessions, gender, and reported ‘‘mild sensitivity to motion sickness in adulthood" (see paragraph ‘‘subjects"). Random effects were modeled using heterogeneous compound symmetry which assumes a similar correlation between residuals of the same subject but no correlation between different subjects. Statistical significance level was defined as $P \leq 0.05$.

Before the balance tasks, subjects performed a neurocognitive test battery (reported elsewhere (van Nierop et al. 2012)) for about an hour in the same three conditions (sham, low, and high exposure, with standardized head movements). Therefore, a sensitivity analysis was run using the average personal exposure to SMFs and TVMFs during the hour prior to the balance tasks in similar mixed-effects models.

5.3 RESULTS

Of the 30 eligible subjects, 28 subjects completed all three experimental sessions; two subjects completed only two sessions. Eventually a total of 69 sessions of 28 subjects were included in the analysis, and 25 sessions were excluded because of missing exposure or postural sway data.

Average personal exposure as measured during the hour of neurocognitive testing and during head movements before both balance tasks in the sham, low and high exposure conditions are shown in Table 1. The mean scores for postural body sway path, area and velocity for the parallel and tandem task in the three conditions are presented in Table 2.

Table 1 Average personal exposure levels (in Tesla) in the assigned sham; low and high exposure conditions as measured in the hour prior to the balance tasks, during the head movements (about 16 seconds) before the parallel task, and head movements (about 16 seconds) before the tandem task (N=28).

		Sham (28)			Low (20)			High (21)		
Time period	Field	Mean	GM	GSD	Mean	GM	GSD	Mean	GM	GSD
Hour before balance task	B_o	0.01	0.01	2.26	0.46	0.46	1.14	0.78	0.77	1.14
	dB/dt	0.02	0.02	2.49	0.21	0.20	1.21	0.37	0.37	1.17
Head movements before parallel task	B_o	0.01	0.01	1.24	0.24	0.24	1.14	0.37	0.37	1.15
	dB/dt	0.02	0.02	1.34	0.50	0.48	1.36	0.71	0.70	1.22
Head movements before tandem task	B_o	0.01	0.01	1.24	0.24	0.24	1.15	0.36	0.36	1.12
	dB/dt	0.02	0.02	1.34	0.47	0.45	1.35	0.68	0.67	1.19

Note. All data represent raw, untransformed data.
Abbreviations: (GM) Geometric Mean (GSD) Geometric Standard Deviation
(28/20/21): number of subjects in calculation

Table 2 Average test performance on postural sway for the balance task in parallel and tandem position in the sham; low and high exposure conditions (N=28).

		Sham (28)			Low (20)			High (21)		
Test	Sway	Mean	GM	GSD	Mean	GM	GSD	Mean	GS	GSD
Parallel	Path	10.7	9.72	1.49	23.0	13.6	2.54	18.6	13.0	2.12
	Area	125	107	1.66	203	136	2.34	236	149	2.39
	Velocity	16.3	14.8	1.48	29.6	19.3	2.36	27.5	19.3	2.13
Tandem	Path	50.5	34.3	2.45	66.9	41.7	2.80	81.1	56.0	2.47
	Area	368	244	2.56	514	324	2.83	683	439	2.67
	Velocity	84.4	59.5	2.38	115	67.3	3.06	143	101	2.37

Note. All data represent untransformed data; statistical analyses were done on log-transformed data. Abbreviations: (GM) Geometric Mean (GSD) Geometric Standard Deviation (28/20/21): number of subjects in calculation. Sway path in mm, Sway area in mm^2, Sway velocity in mm/s

Figures 4 and 5 depict the unadjusted results for postural body sway path, area, and velocity in the parallel and tandem tasks according to personal exposure to the SMF and TVMF. In addition, Table 3 presents the adjusted mixed model results of the relationship between personal exposure to SMFs, TVMFs, and postural body sway. Increasing SMF exposure in the balance task with feet in parallel position showed an increase in sway path (P=0.008), sway area (P=0.008), and sway velocity (P=0.013) (Table 3). Similarly, TVMF exposure was associated with reduced performance on the parallel task, i.e., increased sway path (P=0.015), area (P=0.018), and velocity (P=0.025).

When feet were in tandem position a similar increase in sway was seen, which appeared to be only statistically significant association for exposure to the SMF and sway area (P=0.023) (Table 3). For sway path (P=0.095) and sway velocity (P=0.090), the association reached only borderline significance. TVMF exposure was not statistically significantly associated with postural sway (path P=0.232, area P=0.063, or velocity P=0.200), although balance performance was reduced with increasing exposure.

A sensitivity analysis was performed using the average personal SMF and TVMF exposure levels during the hour of cognitive testing prior to the balance tasks in the sham, low, and high exposure conditions. These average hourly exposure measures were strongly correlated with the individual exposure levels during the head movements before the balance tasks (r =0.969 and r=0.992 for SMF of the parallel and tandem task respectively, and r=0.930 and r=0.985 for TVMF of the parallel and tandem task, respectively). There was comparable variation across the sham, low, and high exposure conditions. In line with these observations, these sensitivity analyses resulted in similar trends compared to the main analysis (see Supplemental Information Table S1).

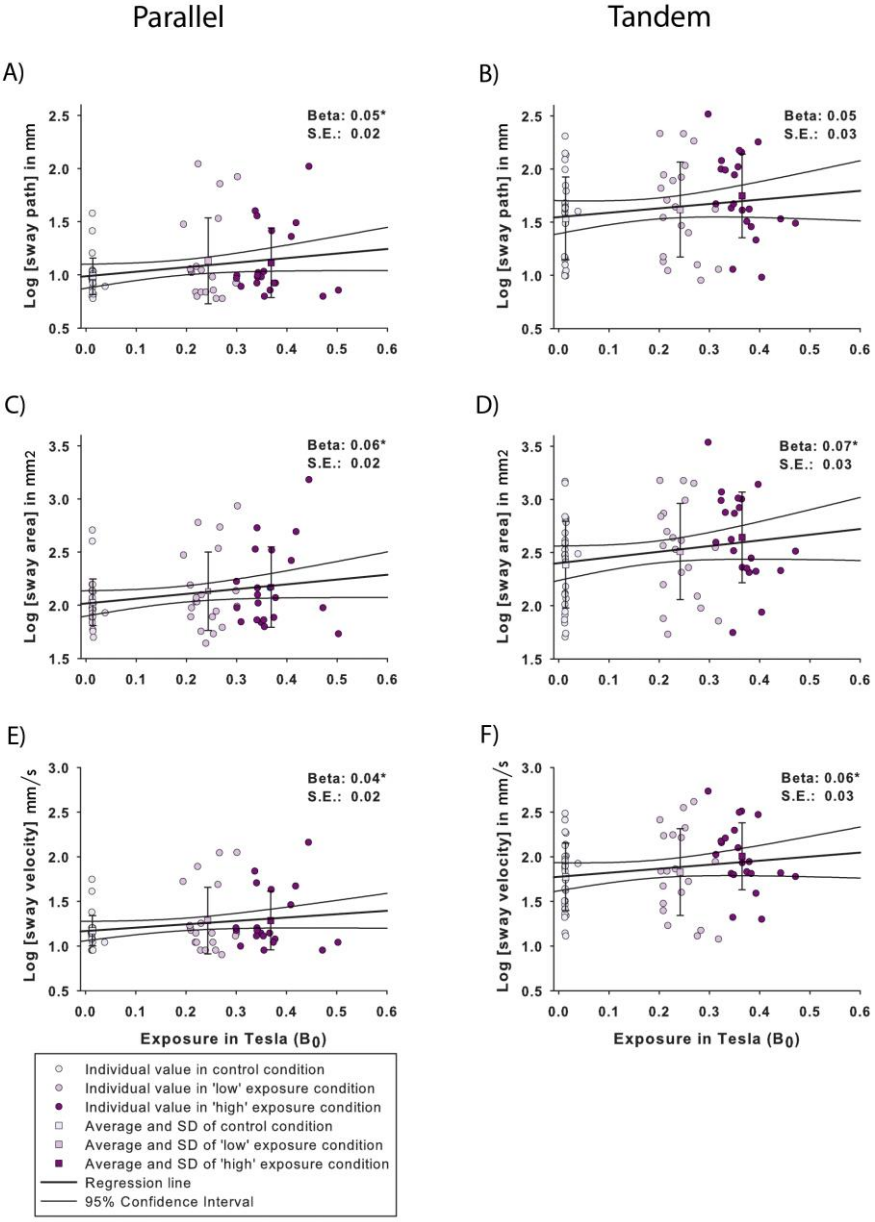


Figure 4 Postural body sway path (A), area (C) and velocity (E) in the parallel task and sway path (B), area (D) and velocity (F) in the tandem task in relation to static magnetic field exposure (SMF). Each dot represents a single subject (N=28, with 69 subject observations) in one of the three exposure conditions (sham white, low exposure light grey, high exposure black). Unadjusted regression lines with corresponding 95% confidence intervals are based on all data points. The regression coefficient (beta) of the *unadjusted* model is calculated per 100 mTesla with corresponding standard error. Group averages in the control, low and high exposure conditions are depicted by the squares with corresponding standard error bars.

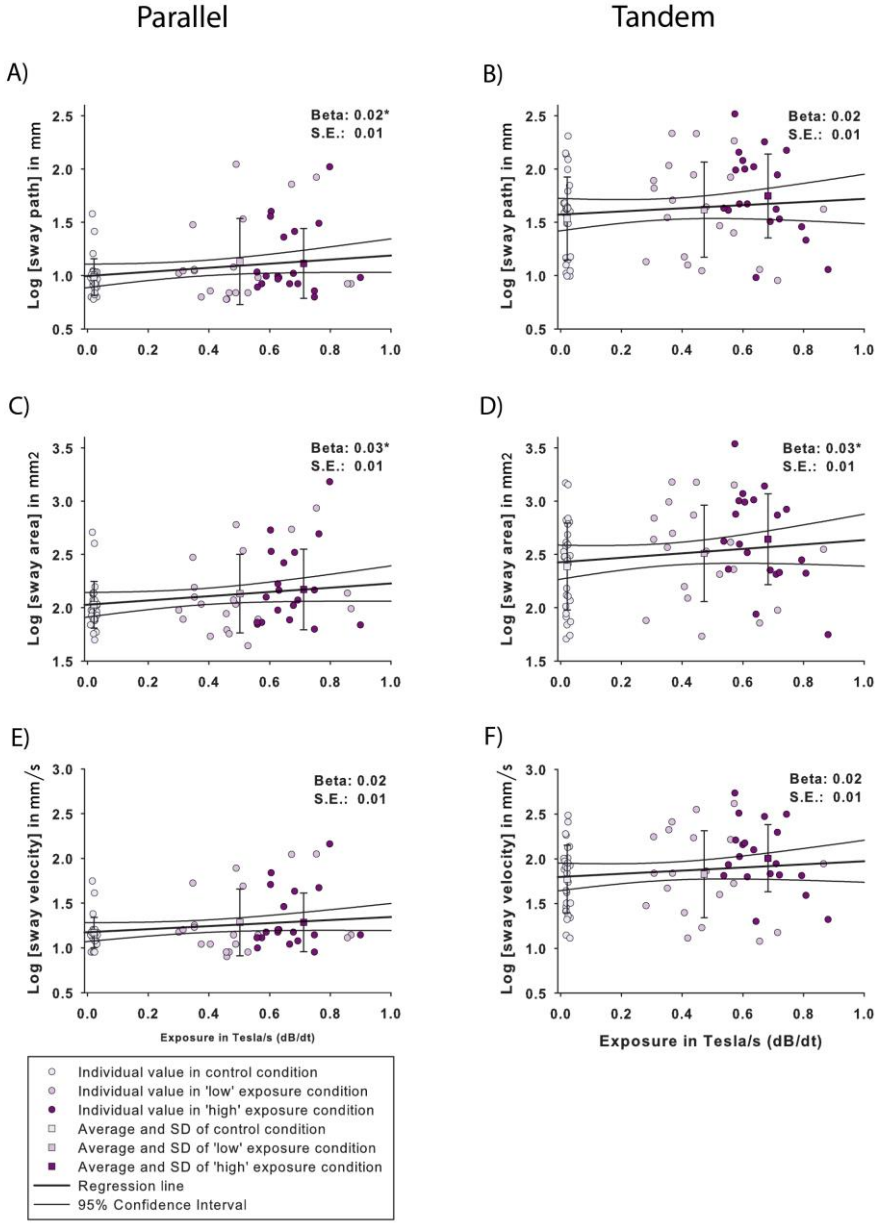


Figure 5 Postural body sway path (A), area (C) and velocity (E) in the parallel task and sway path (B), area (D) and velocity (F) in the tandem task in relation to time-varying magnetic field exposure (TVMF). Each dot represents a single subject (N=28, with 69 subject observations) in one of the three exposure conditions (sham white, low exposure light grey, high exposure black). Unadjusted regression lines with corresponding 95% confidence intervals are based on all data points. The regression coefficient (beta) of the *unadjusted* model is calculated per 100 mTesla with corresponding standard error. Group averages in the control, low and high exposure condition are depicted by the squares with corresponding standard error bars.

Table 3 Estimated trends of test performance per 100 mTesla for the SMF and per 100 mTesla·s^{-1} for the TVMF using personal exposure data measured during head movements before the parallel task (A) and tandem balance task (B) (N=28, with 69 subject observations).

A) Parallel task

		Intercept			Exposure			
Field	Sway	Estimate	5% CI	95% CI	β per 100 mT (·s^{-1})	5% CI	95% CI	P
SMF	Path	0.809	0.618	1.000	0.060	0.016	0.104	**0.008**
	Area	1.860	1.654	2.066	0.066	0.018	0.114	**0.008**
	Velocity	0.998	0.805	1.191	0.056	0.012	0.100	**0.013**
TVMF	Path	0.831	0.642	1.021	0.028	$5.60E^{-3}$	0.050	**0.015**
	Area	1.890	1.684	2.096	0.029	$5.31E^{-3}$	0.053	**0.018**
	Velocity	1.022	0.831	1.213	0.025	$3.39E^{-3}$	0.047	**0.025**

B) Tandem task

		Intercept			Exposure			
Field	Sway	Estimate	5% CI	95% CI	β per 100mT (·s^{-1})	5% CI	95% CI	P
SMF	Path	1.611	1.273	1.948	0.049	$-8.96E^{-3}$	0.107	0.095
	Area	2.431	2.084	2.778	0.068	0.010	0.127	**0.023**
	Velocity	1.878	1.538	2.219	0.051	$-8.45E^{-3}$	0.111	0.090
TVMF	Path	1.649	1.310	1.987	0.018	-0.012	0.048	0.232
	Area	2.461	2.112	2.810	0.029	$-1.64E^{-3}$	0.059	0.063
	Velocity	1.913	1.572	2.253	0.020	-0.011	0.051	0.200

Abbreviations: (CI) Confidence Interval; (SMF) Static magnetic field; (TVMF) Time-varying magnetic field. Sway path in log(mm), Sway area in log(mm^2), Sway velocity in log(mm/s).
Note. All data represent back transformed data. Model was adjusted for order of sessions, gender, and motion sickness. 'Adjusted for motion sickness' includes subjects with 'mild' motion sickness symptoms (n=8), defined as a score of 2 on a 4 point Likert scale ranging from 1 (not at all) to 4 (very often) for at least one of three types of symptoms (see paragraph 'subjects').

5.4 DISCUSSION

In this study, we aimed to characterize acute effects on postural body sway of exposure to head movement induced TVMFs in the SMF of a 7.0 T MRI magnet. Results indicated a reduced postural stability with increasing levels of exposure in healthy volunteers. The assessed balance task showed an increased sway path, area, and velocity after exposure to SMFs in combination with TVMFs when feet in parallel position and eyes closed. With feet in tandem position and eyes closed similar effects were seen, but only sway area was statistically significantly associated with SMF exposure. These findings support the hypothesis that (movement in) a spatially heterogeneous SMF negatively affects postural body sway.

We assessed two relatively difficult versions of the balance task (better known as the Romberg test) as we aimed to pick up subtle changes in performance in a young and healthy subject population. The balance task with feet in parallel position and eyes closed is relatively easier to perform than the version with feet in tandem position and eyes closed. As expected, the parallel version proved to be easier to finish successfully and showed less random variability in our study, hence making it easier to assess effects of exposure. The postural body sway endpoints used - path, area and velocity - are highly correlated. However, these measures can differ from each other. For example, in our study subjects accomplished a comparable path and velocity, but tended to have a higher area in the tandem task when exposed to the MFs.

It remains unclear whether exposure to SMFs, motion induced TVMFs, or the combination of both, is responsible for the observed effects on postural body sway. Analyses in the current experiment were performed with exposure to either SMFs or TVMFs as exposure variables. However, exposure occurred simultaneously so the effects of SMFs and TVMFs could not be disentangled. Though, efforts should be made to address this in future studies, as should be the effects of timing, duration, and direction (orientation relative to the field lines) of exposure on postural stability.

Several lines of research address a possible explanation for acute effects on standing balance. It has previously been postulated that strong MFs of MRI scanners interact with the vestibular apparatus of the human inner ear (de Vocht et al. 2007; Glover et al. 2007; Schenck 2000; Schenck et al. 1992). Behavioral studies in rodents have demonstrated a role of the vestibular organ in the perception of MFs.

For example, normal rats avoided entering a 2 T SMF while labyrinthectomized rats simply entered a 14.1 T SMF (Houpt et al. 2007; Weiss et al. 1992). Furthermore, above 7.0 T exposure conditioned taste aversion (Houpt et al. 2003; Nolte et al. 1998) and circling locomotor activity was induced in normal rats compared to the labyrinthectomized rats (Houpt et al. 2003; Lockwood et al. 2003; Nolte et al. 1998; Snyder et al. 2000), where the direction of circling was dependent on the spatial position of the rat within the MF. Recently is has been demonstrated that normal rats within a 14.1 T MRI tilt their heads depending on the orientation of the MF (Houpt et al. 2012). In addition, normal rats had an increased c-Fos expression (indicating neuronal activity) after MF exposure in nuclei associated with the vestibular system (Cason et al. 2009; Snyder et al. 2000). Based on these animal results, it seems likely that the vestibular organ is affected by strong MFs. However, the exact working mechanism and which part of the vestibular organ is involved is not clear since both the semicircular canals and otolith organs are destroyed by chemical labyrinthectomy (Cason et al. 2009).

Few human studies have been conducted and they showed less clear evidence of vestibular disturbance when exposed to SMFs. Performance on the caloric reflex test was not affected after exposure to SMFs of 2–7 mT (Winther et al. 1999) nor after exposure to a stronger MF of 9.4 T for 30 min in a small pilot study with healthy volunteers (Patel et al. 2008). A recent study by Roberts et al. in healthy volunteers suggested that a strong SMF elicits directiondependent nystagmus when entering/exiting a 3.0 or 7.0 T MRI (Roberts et al. 2011). The speed of movement did not increase or enhance the nystagmus suggesting that only the SMF is responsible for inducing nystagmus. Other human experiments in contrast, pointed to acute effects of movement in such SMF. These experiments showed acute effects of movement induced TVMFs in the SMF of an MRI magnet, indicating a decreased cognitive functioning (de Vocht et al. 2007; de Vocht et al. 2003; de Vocht et al. 2006b; van Nierop et al. 2012) and sensory effects such as nausea, vertigo, metallic taste, and a sensation of movement (de Vocht et al. 2006b; Glover et al. 2007). These symptoms are very similar to the symptoms that occur upon galvanic stimulation of the vestibular system (Fitzpatrick et al. 2004). In addition, experiments with standing or moving subjects in a SMF demonstrated that only moving subjects in a SMF reported vestibular-related symptoms (Glover et al. 2007). In practice, such symptoms could be limited by decreasing the rate and frequency of movement within the static magnetic stray field (de Vocht et al. 2006b).

Taking together previous results and the current effects on postural stability, two possible mechanistic explanations seem plausible, which could also co-exist. On the one hand, it is conceivable that exposure to the MFs elicit a change in cognitive functions, which in turn affects postural stability (Pellecchia 2003; Weeks et al. 2003), since standing balance (stabilometry) depends on proprioceptive, visual, vestibular, and cognitive information (Nashner 1997). On the other hand, it is also possible that SMFs, TVMFs or the combination of both can interact with (parts of) the vestibular system since a disturbed vestibular system can result in a changed postural stability, changed cognitive functioning (Utz et al. 2010), and sensory symptoms (Brandt et al. 2005). So far, a few (theoretical) working mechanisms have been proposed, of which direct nerve stimulation by electromagnetic induction (movement in an MF induces an electrical current) seems the most plausible (Glover et al. 2007).

Alternatively, diamagnetic susceptibility of molecules or magnetohydrodynamic currents in the fluid of the vestibular system could lead to a changed perception and function (Glover et al. 2007; Patel et al. 2008). A more recently developed model proposes that Lorentz forces can act as a component of the magnetohydrodynamic condition resulting in a continuous current within the endolymph fluid of the labyrinth (Roberts et al. 2011).

Strengths of our experiment included a balanced double- blind randomized crossover design. As individuals served as their own controls, this design corrects for large interindividual differences in postural sway. Nevertheless, some limitations need to be taken into account. Several measures were taken to develop a double-blind setup, such as an audiotape playing the acoustic noise of an MRI system (in stand-by mode) in the sham condition, and blind-guiding of the subject and experimenter into and out of a standardized tent where they were tested. However, blinding was not perfect since three out of 11 subjects with a splint behind their teeth reported they could feel the MF because their splint was apparently made of a weak paramagnetic material, undetected by the metal detector. A re-analysis of the data without these three subjects resulted in similar conclusions, yet for SMF and TVMF exposure slightly higher effect estimates and smaller P-values on postural sway path, area, and velocity in the tandem task were observed (see Supplemental Information, Table 2).

Based on the post-session questionnaires, perceived ‘‘exposure" versus ‘‘no exposure" reported by the remaining 26 subjects after the sham, low, and high

exposure conditions was correct in 68, 36, and 64% of the sessions, respectively. Test leaders were also asked to indicate perceived "sham," "low," or "high" exposure after each session and had 93, 62, and 42% correct predictions, respectively. The test leader rates are more difficult to interpret since they attached the balance belt to the subject and the belt contained a weak paramagnetic material, which could have revealed the exposure condition to the test leaders, but not to the subjects. However, test leaders' knowledge about the exposure condition is not expected to significantly influence a subject's task performance as recording was started by the experiment coordinator and scoring of sway parameters was done automatically by the monitoring device. Nevertheless, blinding in future studies can be improved by refining the setup and specifically enquiring about magnetic splints prior to enrollment.

The potential practical (safety) implications of acute effects of exposure to strong MFs on standing balance, and hence performance of, e.g., surgeons performing MRI-guided operations, need to be investigated. Exposure levels as examined in this experiment occur in practice. Moreover, most surgeons and personnel are in standing position during MRI-guided interventional procedures. Therefore, the present results on standing balance should be taken into account in the safety procedures concerning MRI-guided surgery.

For comparison, the percent increase in postural body sway area due to SMF and TVMF exposure found in this study is of a similar magnitude as the percent increase reported in an experiment with subjects standing on a force plate with a blood alcohol concentration of around 0.09% (Ando et al. 2008). This concentration is comparable to five alcoholic drinks (one unit of alcohol in UK= 8 g ethanol) for an adult male of 80 kg (Jones et al. 2009) and is well above the legally allowed maximum blood alcohol concentration for driving.

In conclusion, the results of this study imply that exposure to MRI-related MFs at levels that are experienced in practice, can result in an acute increased postural body sway.

ACKNOWLEDGMENTS

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SUPPLEMENTAL MATERIAL

Table S1 Analyses with alternative exposure measures. Estimated trends of test performance per 100 mTesla for the SMF and per 100 mTesla·s^{-1} for the TVMF using personal exposure in the hour prior to the balance task for the parallel task (A) and the tandem task (B) (N=28, with 69 subject observations).

A) Parallel task

Field	Sway	Intercept			Exposure			
		Estimate	5% CI	95% CI	β per 100 mT(·s^{-1})	5% CI	95% CI	P-value
	Path	0.846	0.652	1.039	0.023	2.18 E^{-3}	0.043	**0.031**
SMF	Area	1.886	1.680	2.092	0.027	4.84 E^{-3}	0.049	**0.018**
	Velocity	1.031	0.835	1.226	0.021	8.45 E^{-4}	0.042	**0.042**
	Path	0.789	0.593	0.985	0.061	0.018	0.104	**0.006**
TVMF	Area	1.815	1.608	2.023	0.074	0.028	0.120	**0.002**
	Velocity	0.970	0.772	1.168	0.060	0.017	0.103	**0.008**

B) Tandem task

Field	Sway	Intercept			Exposure			
		Estimate	5% CI	95% CI	β per 100 mT(·s^{-1})	5% CI	95% CI	P-value
	Path	1.597	1.266	1.927	0.027	1.13 E^{-4}	0.055	**0.049**
SMF	Area	2.419	2.081	2.756	0.037	0.010	0.064	**0.008**
	Velocity	1.865	1.532	2.199	0.028	3.45 E^{-4}	0.056	**0.047**
	Path	1.563	1.221	1.905	0.063	1.92 E^{-3}	0.123	**0.043**
TVMF	Area	2.383	2.034	2.733	0.080	0.20	0.141	**0.010**
	Velocity	1.824	1.480	2.168	0.067	5.16 E^{-3}	0.129	**0.034**

Abbreviations: (CI) Confidence Interval; (SMF) Static magnetic field; (TVMF) Time-varying magnetic field. Sway path in log(mm), Sway area in log(mm^2), Sway velocity in log(mm/s).
Note. All data represent back transformed data. Model was adjusted for order of sessions, gender, and motion sickness. 'Adjusted for motion sickness' includes subjects with 'mild' motion sickness symptoms (n=8), defined as a score of 2 on a 4 point Likert scale ranging from 1 (not at all) to 4 (very often) for at least one of three types of symptoms (see paragraph 'subjects').

Table S2 Sensitivity analysis excluding subjects (N=3 with 8 subject observations) with splint who could feel the presence/absence of the magnetic field exposure: Estimated trends of test performance per 100mTesla for the SMF and per 100 mTesla·s^{-1} for the TVMF using personally measured exposure during head movement before the parallel task (A) and the tandem task (B) (N=25, with 61 subject observations).

A) Parallel task

Field	Sway	Intercept			Exposure			
		Estimate	5% CI	95% CI	β per 100 mT(·s^{-1})	5% CI	95% CI	P-value
	Path	0.791	0.581	1.001	0.059	0.011	0.107	**0.018**
SMF	Area	1.843	1.619	2.066	0.061	9.78 E^{-3}	0.112	**0.021**
	Velocity	0.980	0.766	1.194	0.054	5.45 E^{-3}	0.102	**0.030**
	Path	0.803	0.595	1.012	0.059	0.011	0.107	**0.018**
TVMF	Area	1.864	1.640	2.088	0.061	9.78 E^{-3}	0.112	**0.021**
	Velocity	0.992	0.781	1.204	0.054	5.45 E^{-3}	0.102	**0.030**

B) Tandem task

Field	Sway	Intercept			Exposure			
		Estimate	5% CI	95% CI	β per 100 mT(·s^{-1})	5% CI	95% CI	P-value
	Path	1.462	1.123	1.800	0.059	6.21 E^{-3}	0.112	**0.030**
SMF	Area	2.289	1.937	2.641	0.074	0.020	0.127	**0.009**
	Velocity	1.715	1.378	2.053	0.062	0.011	0.113	**0.018**
	Path	1.484	1.142	1.826	0.025	-2.50 E^{-3}	0.053	0.073
TVMF	Area	2.307	1.952	2.663	0.033	4.76 E^{-3}	0.061	**0.023**
	Velocity	1.735	1.395	2.075	0.027	6.49 E^{-4}	0.054	**0.045**

Abbreviations: (CI) Confidence Interval; (SMF) Static magnetic field; (TVMF) Time-varying magnetic field. Sway path in mm, Sway area in mm^2, Sway velocity in mm/s.
Note. All data represent back transformed data. Model was adjusted for order of sessions, gender, and motion sickness. 'Adjusted for motion sickness' includes subjects with 'mild' motion sickness symptoms (n=8), defined as a score of 2 on a 4 point Likert scale ranging from 1 (not at all) to 4 (very often) for at least one of three types of symptoms (see paragraph 'subjects').

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Chapter 6

MRI-related static and head movement-induced time-varying magnetic fields; nystagmus and effects on oculomotor functions and postural stability

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ABSTRACT

We investigated effects of exposure to static magnetic fields (SMF) with or without additional head movement-induced time-varying magnetic fields (TVMF) near a 7-T MRI scanner on vestibular related functions of nystagmus, oculomotor function and postural stability. In a double-blind, sham-controlled randomized crossover experiment 36 healthy subjects underwent four test sessions, two exposure conditions and two corresponding sham conditions. The two exposure conditions consisted of 1.0 T SMF either with or without additional head movements inducing a TVMF of 2.4 T/s immediately before each task. The test battery assessed nystagmus, oculomotor functions and postural stability. Saccadic eye movement velocity was increased ($p<0.05$) in both exposure conditions compared to their sham conditions. Stability in the parallel tasks was (borderline) significantly improved in SMF+TVMF condition compared to sham+HM ($p=0.01$ and $p=0.07$). Smooth pursuit eye movements were not affected by exposure and no nystagmus could be detected in any of the conditions. The increased saccadic eye velocity induced by SMF exposure is most likely caused by small saccadic jumps. Further research is needed to replicate results on saccadic and postural functions. No other effects of SMF or SMF+TVMF on vestibular related outcomes could be demonstrated which would indicate a role of the vestibular system.

6.1 INTRODUCTION

Magnetic resonance imaging (MRI) is an imaging technique with a broad range of applications in clinical and medical research. The magnetic fields present during scanning are regarded as non-invasive and safe for patients and employees (ICNIRP 2014). Despite this, employees working in the vicinity of MRI scanners in stand-by modus, report transient sensory complaints like nausea, vertigo, dizziness and a metallic taste while being exposed (Schaap et al. 2014). Earlier experimental research found that postural instability (van Nierop et al. 2013) and cognitive effects were induced when moving in front of the scanner bore (de Vocht et al. 2003; de Vocht et al. 2006; van Nierop et al. 2014b; van Nierop et al. 2012) and herewith exposed to a combination of static magnetic stray fields (SMF) and low-frequency motion-induced time-varying magnetic fields (TVMF). These cognitive effects (i.e. decreased memory, visuomotor performance, attention and concentration) were not present when motionless and consequently exposed to the stray SMF only (van Nierop et al. 2014b) or when in the homogeneous field inside the scanner bore (Heinrich et al. 2013; Lepsien et al. 2012) compared to sham.

An underlying working mechanism resulting in these transient symptoms and effects has not been established yet. It has been postulated that the vestibular system might play an important role (Glover et al. 2007; Roberts et al. 2011). Lorentz forces resulting from exposure to SMF interact with the ionic current of the endolymph fluid in the semi-circular canals of the vestibular labyrinth. The emerged force in the endolymph fluid pushes against the cupula transducing a signal of head rotation to the vestibular afferents. This would result in involuntary eye movements (nystagmus) through the so-called vestibulo-ocular reflex that normally serves to stabilize images on the retina in case of head movements. Evidence for this mechanism came from computer modelling (Antunes et al. 2012) and experimental studies with lesioned animals (Cason et al. 2009) and patients lacking labyrinthine functions (Roberts et al. 2011; Ward et al. 2014). Also, exposure of healthy volunteers to a homogeneous SMF within the bore of an MRI system has been shown to induce a robust nystagmus (Roberts et al. 2011). Additional TVMF by moving the person in and out the bore on the scanner bed, did not change (the magnitude of) the finding. Therefore, nystagmus but also sensation of nausea and dizziness upon magnetic field exposure point towards involvement of the vestibular system. The postulated deflection of the cupula by SMF induced Lorentz forces

could probably also play a substantial role in oculomotor functions, postural stability and cognitive abilities since there is a direct connection from the vestibular nuclei to eye muscles, spinal cord and higher cortical areas in the brain (Angelaki et al. 2008).

Taken together, there is evidence that exposure to MRI-related homogenous SMF induces nystagmus (Roberts et al. 2011) and exposure to a combination of stray SMF and TVMF leads to postural instability (van Nierop et al. 2013). A plausible (mediating) mechanism involves effects of SMF and/or TVMF exposure on the vestibular system. The primary objective of the current study was to further assess the postulated role of the vestibular system in behavioral effects resulting from MRI-related SMF and TVMF exposure. In order to achieve this goal, several vestibular related endpoints, i.e. nystagmus, oculomotor functions including smooth pursuit and saccadic eye movements as well as postural stability, were experimentally assessed in healthy volunteers. Since exposure to SMF and TVMF might act upon the vestibular system through different biophysical mechanisms, the secondary objective of this study was to separately assess potential behavioral effects from exposure SMF and from exposure to SMF in combination with TVMF. The vestibular related endpoints were tested in a double-blind, sham-controlled randomized cross-over experiment, with two exposure conditions: exposure to SMF and exposure to the combination of these SMF and low-frequency head movement-induced TVMF in the stray SMF of a 7 T MRI scanner.

6.2 METHODS

Subjects

A total of thirty–six healthy volunteers participated in the experiment (6 men and 30 women) with an average age of 22 (ranging from 18 to 30 years; SD 2.74 years). Most of the subjects were students (n=28) recruited with flyers on bulletin boards at Utrecht University. Of all participants, 29 finished pre-university level, 5 finished university and 2 finished lower secondary professional education. Applied exclusion criteria were self-reported presence of MRI-incompatible elements in the body, history of neurological disease, serious vision deficiencies, use of medication (except for birth control), soft or hard drugs and excessive use of alcohol (>2 standard units per day) or coffee (>5 cups per day). The majority of the study population (19 subjects) had never seen an MRI scanner before, 13 subjects had undergone an MRI scan once, 2 subjects twice, 1 subject three times and 1 subject five times. However, none of the volunteers had worked with MRI or had seen the specific 7 T MRI room before. Individual subjective sensitivity to motion sickness was defined by a short version of the MSSQ (Golding 1998) where not prone (score <3), moderately prone (score 4-6) and highly prone (score >6) to motion sick was defined on a 12-point Likert scale. Subjects were asked to abstain from alcohol 24 hours and caffeine 3 hours before the experiment. The study was approved by the local medical ethics research committee of the University Medical Center Utrecht (UMCU), the Netherlands.

Experimental design

A double-blind, sham-controlled randomized crossover design was used in which each subject was tested in a practice session and four experimental sessions on two consecutive days, see figure 1A. A single session took on average 15 minutes and was conducted on the same time of each day for a specific subject.

To ensure a double-blind experiment, subjects and experimenter were blind-guided by the experiment coordinator (LvN) into a standardized tent (210x140x90 cm). Clothing and test equipment contained no ferromagnetic components to prevent subject and experimenter from perceiving attractive forces. In addition, an audio file playing the acoustic noise of an MRI system was used in the sham room.

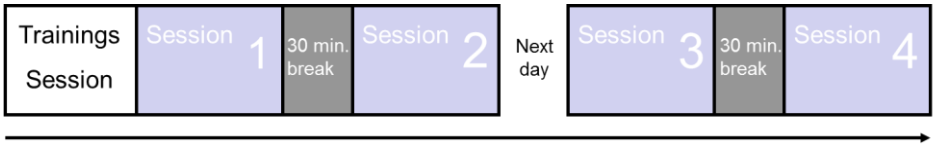
Of the four experimental sessions, two were exposure conditions in the stray field of a passively shielded 7.0 T Philips Achieva research system located at

University Medical Center Utrecht. In one exposure condition subjects were exposed to 1.0 T SMF only ('SMF') and in the other exposure condition to a combination of 1.0 T SMF and 2.4 T/sec TVMF ('SMF+TVMF'). These TVMF were induced before every single test by standardized head movements by the subject covering an angle of 180 degrees in 0.8 s, ten in horizontal and ten in vertical direction and the start of each movement was indicated by an auditory cue (van Nierop et al. 2014a). To standardize the exposure to 1.0 T SMF, the subject sat on a fixed chair with the back towards the bore in the center line at 47 cm from the MRI magnet. For the postural stability tasks the subject had to stand on a marked spot in the tent in the center line at 90 cm in front of the scanner, resulting in a lower SMF and TVMF exposure of respectively 0.37 T and 0.70 T/s at head height while standing. There were also two corresponding unexposed sham conditions (SMF exposure <0.025T) in a separate room; one without ('sham') and one with similar standardized head movements ('sham+HM'), respectively. The order of the two exposure and two sham conditions were randomized within a day. The order of the two paired exposure or two paired sham sessions was randomized for all subjects.
Before each session, subjects were asked to complete a questionnaire about current symptoms. A short questionnaire on (adverse) side effects and subjects perception of whether they thought exposure had been present was completed after each session by both subjects and experimenter.

Test battery and data recording

The test battery consisted of a series of standardized tasks to assess, oculomotor, vestibular and postural stability functions, see Figure 1B.

A) Set-up of the experiment



B) Content of each session

Time	Task/ activity
0'-18'	Cognitive tasks
18'	Head movement or break
	Smooth pursuit eye movements
	Head movement or break
	Saccadic eye movements
	Head movement or break
	Spontaneous eye movements
	Practice balance task parallel
	Head movement or break
	Balance task parallel
	Practice balance task tandem
	Head movement or break
	Balance task tandem
	Head movement or break
32'	Balance task parallel (90 sec)

Figure 1 Set-up of the experiment (A). Each subject underwent a trainings session followed by 4 experimental sessions. The order of the two exposure and two sham conditions were randomized within a day. The order of the two paired sessions was randomized for all subjects. The test battery took on average 15 minutes and included five different tasks for oculomotor, vestibular and postural stability functions as specified (B). Subjects started with this test battery after performing a series of cognitive tasks that took 15 minutes in the same exposure condition (van Nierop et al. 2014b).

To test oculomotor functions, smooth pursuit and eye saccades were assessed by active tracking/fixating a visual stimulus in the horizontal plane over 10 degrees to each side. The stimulus was presented as a yellow circle with diameter of 1° on a black screen. Only 6 cycles were recorded since a learning effect occurs in pursuit and saccades by ongoing visual feed-back (Barnes 2008; Iwamoto et al. 2010). The sinusoidal pursuit stimulus moved at 0.2 Hz with a peak velocity of 12.6°/s. The outcome measures of *gain* was defined as the ratio of eye velocity to target velocity in percent and *phase* was defined as the shift between eye and target motion

as a function of frequency in degrees per second (Van Der Stappen et al. 2000). The saccadic stimulus was presented 10 degrees to the right, to the middle and 10 degrees to the left at random interval times. Outcome measures of peak velocity, accuracy and latency were derived using algorithms as generally accepted in clinical diagnostic equipment (Van Der Stappen et al. 2000). The peak velocity of the fast phase was calculated in degrees per second. The *accuracy* was defined as the ratio of actual amplitude divided by the target amplitude in percent. The *latency* was defined as the delay between the start of the target movement and the initiation of eye displacement in msec. To assess labyrinth functions, a response by the vestibular-ocular reflex (VOR) was investigated by recording horizontal spontaneous eye movements defined as the slow phase of the nystagmus, in degrees per second, during 30 seconds with imagined visual fixation in darkness and eyes closed.

For stabilization a headrest was used during recordings. Eye movements were recorded by horizontal electro-oculography of both eyes using three disposable electrodes (Blue sensor-N, AMBU, Denmark) of which one was attached at the outer side of the left and right eye and a reference electrode at the forehead. Data was registered and analyzed by BalanceLab software (Balance Lab, Jaeger-Toennies, Wurzburg and Maastricht Instruments v2.3.0.). Saccadic components were removed from smooth pursuit recordings using median filtering. In several electrooculography (EOG) recordings, signal analysis was hampered by a small but substantial 50 Hz frequency sinusoidal noise on top of the EOG signal, which was shown to be induced by electro-magnetic interference in the exposure conditions. The 50 Hz component was therefore eliminated using inverse Fourier band filtering applied in all recordings in the sham and exposure conditions.

To assess postural stability, a standardized Romberg test (Black et al. 1982) was performed for 30 seconds by standing barefoot with arms alongside the body and eyes closed at two levels of increasing difficulty, i.e. with feet in parallel and tandem position. For the task with feet in parallel position also two task durations were assessed, respectively for 30 and 90 seconds. Total body sway path (in mm/sec), average body sway velocity (in mm/s^2) and total covered body sway area (in mm^2/sec) were estimated based on the sum of the body sway in x, y and z direction. Postural stability was recorded by using a small accelerometer (83×51×9 mm, 47 gram) (DynaPort MiniMod, McRoberts Inc., the Netherlands) containing three orthogonal oriented linear accelerometers. The meter was integrated in an elastic belt which was worn around the waist with the device located at the back close to the center of body

mass. The output signals were sampled with a frequency of 100 Hz, 16 Bits, and a resolution of 0.3° (5.5 mG (1 mG≈ cm/s^2)). Data was stored on a removable SD card and processed by special software (MiRA® version 1.9.1, McRoberts Inc., the Netherlands).

Data analysis

Statistical analyses of inter-individual and intra-individual differences in test performance in association with exposure were performed using linear mixed effects models in IBM SPSS Statistics 20.0. Marginal mean test performance of all participants was estimated for each of the conditions as follows:

$$\begin{aligned}\text{Marginal mean} = {} & \text{Intercept} + R.C._{\text{exposure condition}} + 0.25*(\textstyle\sum R.C._{\text{Session1-4}}) + \\ & (0.17*R.C._{\text{male}} + 0.83*R.C._{\text{female}}) + \\ & (0.28*R.C._{\text{not motion sick}} + 0.61*R.C._{\text{moderate motion sick}} + \\ & 0.11*R.C._{\text{high motion sick}})\end{aligned}$$

Where R.C. is the regression coefficient of the model for the specific factor.

The model was adjusted for session order (weighing factor of 0.25), level of motion sickness (weighing factor for: not prone to motion sickness 0.28 (N=10/36), moderately prone to motion sickness 0.61 (N=22/36), highly prone to motion sick 0.11 (4/36)) and sex (weighing factor for males= 0.17 (N=6/36) and for females 0.83 (N=30/36)).

Random effects for subjects were modeled using heterogeneous compound symmetry that assumes similar correlation between residuals of the same subject, but no correlation between different subjects. Pairwise comparisons of sham+HM versus sham, SMF versus sham and SMF+TVMF versus sham+HM were estimated. Pearson correlations were estimated for left/right associations in eye movements, sway path/area/velocity measures of the postural stability task and the three different levels of this task. Because of a very high correlation between sway path, velocity and area (Pearson correlation between 0.548-0.774, N=144, $p<0.001$), and similarity in the results related to exposure, only results of the sway path are presented. Differences in performance on the parallel tasks with duration of 30 sec. and 90 sec. were compared by a paired Student's t-test. Data of all postural stability tasks were estimated as sway path in mm/sec in order to compare across tasks with different

duration, and to improve fit of the statistical models data was log(10) transformed prior to statistical analyses. Statistical significance levels were defined as $p<0.05$.

6.3 RESULTS

All thirty-six subjects completed the four experimental sessions, resulting in 144 observations which could be included in the statistical analysis. For eye movement recordings, the test results of two conditions of a single subject were not available for analysis (sham+HM and SMF+TVMF) due to a calibration error.

Unadjusted mean test scores and standard deviations for all tasks in the four experimental conditions are presented in Table 1. Average smooth pursuit gain (89%) and phase (-2.6°) in the sham condition are slightly worse than has been reported for healthy subjects aged between 20-60 years, namely close to 100% and 0° respectively (Van Der Stappen et al. 2000). For saccadic eye movements the peak velocity (400 degrees per sec), accuracy (95%) and latency (110 ms.) in the sham condition were comparable with those of healthy volunteers aged between 20-60 years (Van Der Stappen et al. 2000). Recordings in darkness with eyes closed did not reveal any pattern of spontaneous horizontal eye movements (nystagmus) neither in the sham conditions nor in the magnetic field exposure conditions. Performances on the postural stability tasks were comparable to that of a normal healthy subject population (Black et al. 1982).

Table 2 shows the marginal mean performance in relation to the exposure conditions for oculomotor functions in the sham, SMF, sham+HM and SMF+TVMF condition, based on a mixed model analysis, adjusted for session, gender, and reported motion sickness. Smooth pursuit eye movements were not significantly affected when subjects were exposed to SMF or SMF+TVMF. The smooth pursuit gain showed a slight non-significant improvement when exposed. The pursuit phase showed a larger variance in performance when exposed to magnetic fields. Saccadic peak eye velocities and accuracy in left and right direction were moderately to strongly correlated (Pearson correlation respectively 0.65 and 0.61 N=141). When exposed to magnetic fields an increased peak eye velocity was seen for SMF ($p<0.001$ for both left and right direction) and for SMF+TVMF ($p=0.007$ for left direction and $p<0.001$ for right direction), see Figure 2. Accuracy and latency of saccadic eye movements were not affected in the exposed conditions.

Table 3 displays the separate average estimated test performances of postural body sway in the sham, sham+HM, SMF and SMF+TVMF conditions. As expected, postural stability is poorest when feet in tandem position compared to feet in parallel position (90 s. and 30 s.) resulting in at least three times higher postural sway path on average. There is a significant difference between performance on the 30 and 90 seconds task with feet in parallel position over all conditions. With the 90 seconds task slightly easier to perform than the 30 seconds task ($p=0.025$), possibly due to a learning effect since the 90 sec. task was assessed as the last. Postural stability was decreased (higher values) in all three tasks after performance of head movements (sham+HM and SMF+TVMF compared to sham) reaching borderline significance in the parallel 30 sec task ($p=0.054$). No (additional) effect of exposure to SMF or SMF+TVMF was found when test performance is compared to sham conditions (SMF versus sham and SMF+TVMF versus sham+HM, respectively). An unexpected significant decreased sway path (improved stability) was revealed in the 90 sec. parallel task ($p=0.013$) which was also visible for the 30 sec task, but did not reach statistical significance ($p=0.069$).

Table 1 Unadjusted average test performance, standard deviations (SD) and geometric means (GM) for oculomotor functions and postural stability in the sham condition, sham condition with standardized head movements (sham+HM), static magnetic field condition (SMF) and static magnetic field conditions with time-varying magnetic fields induced by standardized head movements (SMF+TVMF) (N=36)

Task	Measure[1]	sham			SMF			sham+HM			SMF+TVMF		
		Mean	SD	GM	Mean	SD	GM	Mean	SD	GM	Mean	SD	GM
Smooth Pursuit[2]	Gain	89.3	4.8	89.2	90.4	4.7	90.3	89.0	4.6	88.9	90.3	3.9	90.2
	Phase	-2.6	1.4	n.a.	-2.4	3.4	n.a.	-2.5	1.8	n.a.	-1.5	3.8	n.a
Saccades[2]	Velocity-R	396.8	34.1	395.3	447.3	68.7	442.6	400.8	42.0	398.6	431.7	54.1	423.4
	Velocity-L	398.6	38.4	396.8	436.2	45.3	433.9	408.1	47.6	405.5	426.6	52.0	423.4
	Accuracy-R	94.9	3.0	94.8	94.5	5.6	94.3	94.6	5.0	94.5	95.3	4.6	95.2
	Accuracy-L	94.8	4.0	94.7	96.1	4.6	96.0	94.4	4.7	94.3	95.2	6.0	95.0
	Latency	108.7	5.0	108.6	108.9	5.0	108.8	109.2	8.0	108.9	109.1	5.4	108.9
Postural sway path	Parallel (30 s.)	8.7	6.5	6.7	11.0	7.7	8.5	13.0	9.6	9.8	9.2	7.6	6.7
	Parallel (90 s.)	8.1	5.9	6.3	7.9	5.5	6.5	10.8	8.5	7.9	7.0	6.1	5.1
	Tandem	35.9	32.6	22.3	36.1	30.5	24.7	38.4	29.5	25.7	41.2	32.3	27.2

[1]Gain in percent, Phase in degree, Velocity in degrees per second, Accuracy in percent, Latency in milliseconds, Postural sway path Parallel (30 s), Parallel (90 s.) and Tandem all in in mm/sec, Left (L), Right (R), s (seconds)

[2]In the sham+HM and SMF+TVMF condition the observations of one subject are missing (N=35)

Note: No nystagmus could be detected

Table 2 Average oculomotor performance in the sham condition, static magnetic field condition (SMF), sham condition with head movements (sham+HM), and SMF with time-varying magnetic field condition (SMF+TVMF) from a mixed effects model adjusted for session order, gender and self-reported history of motion sickness (N=36).

					95% CI		
Task	Measure		Estimate	St. Error	Lower Bound	Upper Bound	p-value[1]
Smooth pursuit	Gain	sham	89.48	0.74	88.01	90.96	
		SMF	90.29	0.76	88.79	91.79	0.372
		sham+HM	88.98	0.74	87.51	90.46	
		SMF+TVMF	90.20	0.76	88.69	91.70	0.182
	Phase	sham	-2.36	0.47	-3.29	-1.43	
		SMF	-2.48	0.47	-3.42	-1.54	0.838
		sham+HM	-2.52	0.47	-3.45	-1.60	
		SMF+TVMF	-1.48	0.47	-2.42	-0.54	0.087
Saccade	Velocity to right	sham	396.93	7.64	381.74	412.13	
		SMF	440.96	7.74	425.58	456.34	**<0.001**
		sham+HM	404.29	7.64	389.11	419.47	
		SMF+TVMF	435.68	7.85	420.09	451.27	**<0.001**
	Velocity to left	sham	397.6	7.12	383.35	411.75	
		SMF	433.6	7.18	419.29	447.94	**<0.001**
		sham+HM	409.8	7.11	395.60	423.97	
		SMF+TVMF	428.9	7.27	414.42	443.41	**0.007**
	Accuracy to right	sham	94.72	0.73	93.28	96.17	
		SMF	94.52	0.74	93.06	95.98	0.822
		sham+HM	94.69	0.73	93.25	96.14	
		SMF+TVMF	95.26	0.76	93.76	96.76	0.543
	Accuracy to left	sham	94.94	0.76	93.44	96.45	
		SMF	96.03	0.77	93.50	97.56	0.283
		sham+HM	94.56	0.76	93.05	96.06	
		SMF+TVMF	94.83	0.79	93.27	96.39	0.793
	Latency time	sham	108.91	0.82	107.28	110.54	
		SMF	109.22	0.84	107.56	110.88	0.759
		sham+HM	108.64	0.82	107.01	110.27	
		SMF+TVMF	109.00	0.87	107.26	110.73	0.733

Marginal mean test performance of all participants was estimated as described in the section data analysis. In the sham+HM and SMF+TVMF condition the observations of one subject are missing (N=35). Gain in percent, Phase in degree, Velocity in degree per second, Accuracy in percent, Latency in milliseconds

Note: No nystagmus could be detected

[1]p-values were calculated for the SMF versus sham condition, sham+HM versus sham and SMF+TVMF versus sham+HM condition, respectively.

Bold values; statistical significant at least at $p<0.05$

Table 3 Average postural stability performance in the sham condition, static magnetic field condition (SMF), sham condition with head movements (sham+HM), and SMF with time-varying magnetic field condition (SMF+TVMF) from a mixed effects model adjusted for session, gender and motion sickness (N=36).

			95% CI		
Measure	**Condition**	**Estimate**	**Lower Bound**	**Upper Bound**	**p-value**[1]
Parallel	Sham	6.71	5.20	8.67	
30 sec.	SMF	8.34	6.46	10.77	0.246
	sham+HM	9.66	7.48	12.47	0.054
	SMF+TVMF	6.85	5.31	8.86	0.069
Parallel	sham	6.37	4.95	8.18	
90 sec.	SMF	6.34	4.94	8.15	0.986
	sham+HM	7.87	6.13	10.12	0.207
	SMF+TVMF	5.13	3.99	6.60	**0.013**
Tandem	sham	21.53	15.58	29.74	
	SMF	23.28	16.87	32.18	0.720
	sham+HM	26.98	19.51	37.23	0.311
	SMF+TVMF	28.51	20.61	39.41	0.801

Marginal mean test performance of all participants was estimated as described in the section data analysis.

[1]p-values were calculated for the SMF versus sham condition, sham+HM versus sham and SMF+TVMF versus sham+HM condition, respectively.

Analysis is based on log10 transformation, the presented average performance is back transformed.

Postural sway path in mm/sec

Bold values; statistical significant at least at $p<0.05$

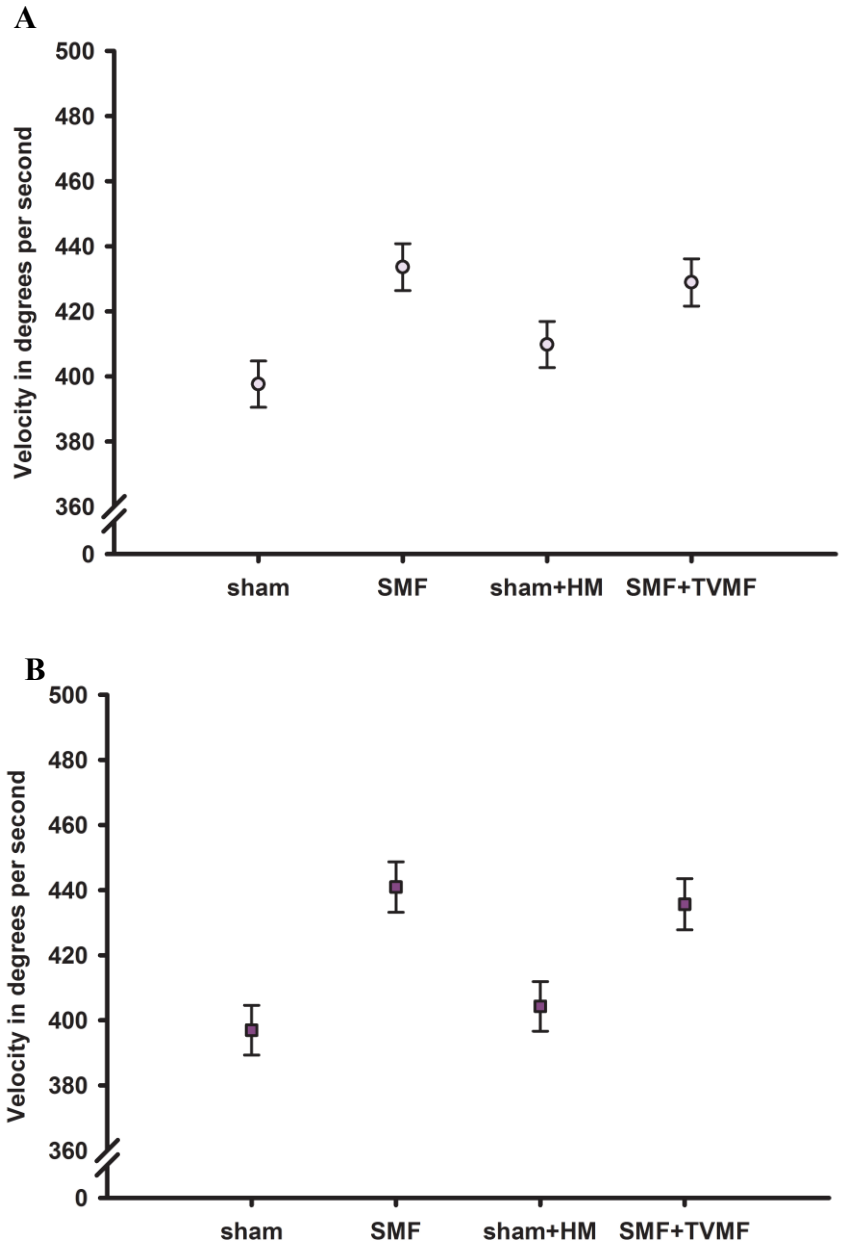


Figure 2 Estimated performance of saccadic eye movements velocity to the right (A) and to the left (B), with corresponding standard errors based on a mixed model analysis in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF) (N=36).

6.4 DISCUSSION

This experiment aimed to further assess the postulated role of the vestibular system in effects of MRI-related static magnetic fields (SMF) and time-varying magnetic fields (TVMF). Therefore, several vestibular related functions were experimentally assessed in healthy subjects, i.e. oculomotor performance of smooth and saccadic eye movements, spontaneous nystagmus, and postural stability. Effects of SMF and the combination of SMF and TVMF were separately studied, as these might differentially affect vestibular performance through different biophysical mechanisms.

Our results showed a statistically significant increased peak velocity of saccadic eye movements in right and left direction when exposed to SMF and when exposed to SMF+TVMF compared to their respective sham conditions. The increase in velocity was more pronounced in the SMF exposure condition (9-11% increased velocity) compared to the SMF+TVMF exposure condition (5-8% increased velocity). There is no indication that the change in saccadic velocity in the SMF+TVMF exposure condition was different than in the SMF exposure condition, suggesting that these changes are driven by exposure to SMF. In contrast, saccadic accuracy and latency time were not significantly affected by exposure to SMF and SMF+TVMF. Also smooth pursuit eye movements were not changed by these exposures. Postural stability was surprisingly not negatively affected but positively affected by exposure to SMF+TVMF. No nystagmus was observed in any of the experimental conditions.

A possible explanation for the found increased saccadic velocity is that the eyes can be considered as a dipole with the positive pole in the front and the negative pole on the back (cornea-retinal potential). The static magnetic field might in theory affect the rotation of the dipole itself and therefore modulate the eye movements. Depending on the orientation of the dipole relative to the magnetic field lines, this would lead to either an increase in eye velocities for eye movements to positions where the orientation of dipole and field lines coincide, or a decrease of eye velocities for eye movements in the opposite direction. Our subjects were located at the negative pole of the MRI magnet with their back towards the bore. The negative charged retina of the eyeball was therefore positioned at the negative side of the scanner. In this situation a pull-push mechanism will attract or repel the eyeball in a way that the positive charged cornea will move towards the scanner bore, resulting in an increased eye movement velocity in left and right direction. This is in line with our findings of increased eye movement velocity in both directions with

almost similar magnitude. The small effects of magnetic field exposure on saccadic velocity that were shown could have consequences for e.g. fMRI examinations and research, where eye tracking is being used. Although a different field line orientation through the body occurs within the bore of an MRI system during fMRI, the experienced static magnetic fields are up to a tenfold stronger, probably inducing a stronger response on oculomotor functions. Further research into possible effects on eye movement velocity would need to take the orientation of the dipole relative to the magnetic field lines into account.

Visual inspection of the recorded electro-oculography signal revealed that in the presence of SMF small (<1 degrees) peaks and jumps occur in the pursuit and saccade curves. These small peaks and jumps did not occur in the sham conditions. After inverse 50 Hz Fourrier filtering or median filtering of the measured signal, these small saccadic like jumps or peaks became even better visible. The small forward saccades were at least partly accounting for the increased velocity as they were in the same direction as the saccades, and especially as they often occurred at maximum saccade velocities. As is custom in normal oculomotor analysis, regular saccadic jumps were filtered out before data extraction. However, a saccadic jump at the top of the curve is not filtered out and will result in an increased peak velocity. Now the key question is, whether this points to an artefact (interference of the magnetic fields with the electro-oculography recording system) or whether these small jumps and peaks in the registration do correlate with real eye movements upon exposure to magnetic fields. Analysis of the obtained calibration values did not show a significant difference between the sham and exposure conditions (paired t-test $p=0.735$ for sham with SMF, and $p=0.496$ for sham+HM with SMF+TVMF). Nevertheless, interference of magnetic fields with the measurement device cannot be ruled out completely and the results on saccadic velocity should therefore be interpreted with due caution.

In theory, also movement of the eye itself as provoked during target tracking, within a magnetic field can induce electrical potentials. However, most likely these currents would be too small to affect smooth eye muscle function and are therefore assumed to be negligible.

A (vestibular-ocular reflex induced) nystagmus would be the most direct indication of effects of SMF and/or TVMF on the vestibular system. However, we were not able to detect a nystagmus in the stray fields of the magnet bore while earlier research demonstrated these spontaneous eye movements inside the magnet

bore of an MRI scanner at three times higher exposure levels of 3.0 T (Roberts et al. 2011). Based on recently developed computer models (Antunes et al. 2012) the cupular pressure difference within a 1.0 T magnetic field is supposed to be around 0.23 mPa, which will result in a 1.4 degree slow phase velocity in the current study. Such a small nystagmus would have been difficult to register with the electro-oculography system we used in our experimental set-up. Therefore, we assume that a stray SMF of 1.0 T as used in our exposure conditions is too low to result in a detectable nystagmus. Moreover, also orientation and geometry of the semicircular canals (SSC) with regard to the magnetic field will define the magnitude of the nystagmus. Nystagmus as demonstrated by volunteers in the scanner bore (Roberts et al. 2011) was induced by SMF with field lines in caudal direction (from head towards the feet), stimulating the lateral (horizontal) semicircular canals herewith inducing a horizontal nystagmus. In our experiment. Subjects sat or stood upright in front of the MRI bore (SMF lines were in anterior direction, from back towards front of the head) since we aimed to mimic occupational exposure of health care workers near an MRI system. In an upright sitting or standing position stimulation of the lateral canals by Lorentz forces is supposed to be stronger than in lying position (Roberts et al. 2011). The absence of a measurable nystagmus in our experimental setting excludes enhancing/reducing effects of spontaneous eye movements on pursuit and saccadic eye movement parameters.

Surprisingly, no detrimental effect of exposure to SMF or exposure to SMF+TVMF was found on performance on the postural stability tasks, especially given our earlier results with respect to SMF in combination with TVMF (van Nierop et al. 2013). Less surprisingly was that the performance of head movements negatively affected postural stability, which has been demonstrated before by Koceja et al. (Koceja et al. 1999). When performing these head movements in the static magnetic field (SMF+TVMF) postural stability improved to values as found in the sham and SMF condition, reaching (borderline) statistical significance in the 30 and 90 sec parallel task. It seems that (some) subjects use the magnetic field as an orientation frame to keep balance. These findings are not in accordance with previous results where exposure to SMF and head movement-induced TVMF showed a significantly decreased postural stability when exposed to an 1.0 T SMF and 2.4 T/s TVMF (van Nierop et al. 2013), see supplemental material S1 for comparison between experiments. Besides the use of different accelerometers, the conflicting results on the postural stability task could also be due to much shorter exposure

duration to SMF and TVMF in the current experiment compared to the previous experiment, 30 versus 65 minutes SMF exposure respectively and 16 versus 21 head movement series for TVMF exposure respectively. With relative short exposure duration (30 min) a small statistically significant positive effect on postural stability was detected while at twice as long exposure duration we saw considerable postural instability.

Strengths of our study included a balanced double-blind randomized crossover design where subjects served as their own controls. A double-blind experimental setup was created by using similar tents, blind guiding of subjects and test leaders into the tents and use of MRI audio recordings in the sham condition. Also a practice session was included to reduce any learning effect in addition to statistical adjustment for session order. Subjects were not informed about the number and order of sham and exposure sessions. Based on a questionnaire at the end of each session, perception of 'exposure' or 'no exposure' was correct in 63% of the sessions by participants (81% in sham, 83% in sham+HM, 22% in SMF, 64% in SMF+TVMF) and 53% by the test leader. The questionnaire also revealed that the subjects indicated 'no exposure' when they did not perceive sensory symptoms. This explains high percentages correct answers in the sham conditions. However, the percentages in the SMF and SMF+TVMF conditions were not statistically significant different from what was expected by chance alone suggesting that blinding of the exposure conditions was successfully applied.

In future research it would be important to see if the current findings can be replicated. In particular with respect to oculomotor functions, future research should concentrate on exposure conditions in (front of) the bore and with different head (and herewith ocular) orientations regarding the magnetic field lines. E.g when a subject turns 180 degrees, facing the MRI scanner at the south pole, no effect is expected from dipole forces. The use of an MRI compatible eye tracking system is preferred in order to measure also vertical and torsional eye movements and to exclude any interference between the magnetic field and measuring devices. The registration of more eye movement cycles per session at different angles, directions, velocity and frequency can be used to get a better understanding and exclude cognitive control. In order to get insight in a possible exposure-response relationship it would be useful to vary in field strength and eventually direction of the magnetic field. Exposure to higher field strengths would possibly also reveal spontaneous eye movements and changed postural stability. For postural stability also duration of

exposure seems to be an important factor therefore longer exposure duration could be applied. However, when studying the effect of TVMF on postural stability it is difficult to exclude the effects of performance of head movement per se since performance of head movement is necessary to induce a TVMF in a SMF.

In conclusion, the results of this study show that saccadic eye velocity was significantly increased when exposed to an MRI-related stray static magnetic of 1.0 Tesla. This effect is most likely attributable to small saccadic jumps, induced by static magnetic field exposure. Postural stability was improved by exposure to a combination of SMF and TVMF. Smooth pursuit eye movements were unaltered by exposure to SMF (1.0 T) or in combination with TVMF (2.4 T/s) during 30 minutes, nor was a nystagmus induced in any of the experimental conditions. A role for the vestibular system in these and previous findings remains unclear. More research into the effects of exposure to MRI-related magnetic fields is warranted.

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SUPPLEMENTAL MATERIAL

Supplemental material 1 Average test performance, standard deviations (SD) and geometric mean (GM) of postural body sway on a postural stability task when feet in parallel and tandem position in the sham+HM and SMF+TVMF conditions of current and previous experiment (van Nierop et al. 2013).

		sham+HM						SMF+TVMF					
		Previous			Current			Previous			Current		
Task	Measure	Mean	SD	GM	Mean	SD	GM	Mean	SD	GM	Mean	SD	GM
Postural	Parallel	10.7	6.54	9.72	13.0	9.6	9.8	18.6	22.33	13.0	9.2	7.6	6.7
sway	Tandem	50.5	48.23	34.3	38.4	29.5	25.7	81.1	75.17	56.0	41.2	32.3	27.2

Sway path in mm/sec.
Previous experiment N=28, Current experiment N=36
The conditions were exactly the same between experiments. Though, in the previous experiment; 1) inclusion criteria of low self-reported vulnerability to motion sickness were applied 2) the total exposure duration was 15 min for the experimental session and 60 min in total 3) a Sensamove measurement device was used. In the current experiment; 1) no inclusion criteria were applied regarding motion sickness 2) the total exposure duration was 15 min for the experimental session and 25 min in total 3) a Dynaport measurement device was used.

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Chapter 7

Does vestibular responsiveness modify acute effects of MRI-related magnetic fields on test performance?

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ABSTRACT

The vestibular system has been postulated to play an important role in acute effects of MRI- related magnetic fields on oculomotor function, cognitive performance and postural stability. Therefore, we investigated whether responsiveness of the vestibular system modifies test performances when exposed to MRI-related static magnetic fields (SMF), with and without time-varying magnetic fields (TVMF). 36 healthy subjects were tested in a randomized, double-blind cross-over experiment with exposure to 1.0 Tesla (T) SMF with and without head movement induced 2.4 T/s TVMF versus sham. Subjects were categorized into relatively high versus normal vestibular responsiveness, based on self-reported sensitivity to motion sickness and measures common in clinical practice, i.e. response to caloric reflex, unilateral weakness, and rotary chair as assessed after the experimental sessions. Unilateral weakness modified the effects of SMF+TVMF exposure on postural stability. Significant but non-coherent modifying effects were found for responsiveness based on MSSQ on several saccadic and pursuit eye movement measures. Effects of magnetic field exposure on cognitive performance were not modified by vestibular responsiveness. Of all potential interactions explored, unilateral weakness seemed to modify the effect of SMF and TVMF on postural stability, indicating that SMF+TVMF exposure improved balance among subjects with high unilateral weakness.

7.1 INTRODUCTION

Exposure to Magnetic Resonance Imaging (MRI) related (stray) static magnetic fields (SMF) is known to induce spontaneous eye movements (nystagmus) (Roberts et al. 2011) and possibly disturbs oculomotor functions (van Nierop et al. submitted). Also a changed postural stability (van Nierop et al. 2013; van Nierop et al. submitted) and decreased cognitive abilities of verbal memory, visuomotor performance and spatial orientation, attention and concentration have been demonstrated when exposed to the combination of SMF and head movement-induced low-frequency time-varying magnetic fields (TVMF) (de Vocht et al. 2007; de Vocht et al. 2006a; de Vocht et al. 2003; van Nierop et al. 2014; van Nierop et al. 2012). Effects of exposure to stray SMF or homogeneous fields (inside the bore of an MRI) alone on cognitive performance were not demonstrated (Heinrich et al. 2013; Lepsien et al. 2012; van Nierop et al. 2014). Moreover, motion sickness related sensory symptoms of vertigo, nausea and dizziness have also been frequently reported and were associated with exposure to magnetic fields of an MRI scanner (de Vocht et al. 2006b; Schaap et al. 2014). Of note, only some individuals report sensory symptoms when exposed to magnetic fields while others never experienced any symptom, possibly modified by speed of movement through the stray magnetic fields around an MRI system (de Vocht et al. 2006b).

It has been hypothesized that exposure to strong magnetic fields affect the vestibular system, which might explain some of the acute effects shown previously. For example, the nystagmus as observed in a SMF arises from direct stimulation of the vestibular labyrinth (Roberts et al. 2011). A theory suggests that Lorentz forces, resulting from exposure to SMF, interact with the ionic current of the endolymph fluid in the semi-circular canals of the vestibular labyrinth. The emerged force in the endolymph fluid pushes against the cupula transducing a signal of head rotation to the vestibular afferents. This results in involuntary eye movements via the so called vestibulo-ocular reflex that normally serves to stabilize images on the retina in case of head movements. Evidence for this mechanism came from computer modelling (Antunes et al. 2012) and experimental studies with lesioned animals (Cason et al. 2009; Ward et al. 2014b) and patients lacking labyrinthine functions (Roberts et al. 2011; Ward et al. 2014a). Deflection of the cupula as induced by magnetic fields can probably also play a substantial role in earlier found changes in oculomotor functions (van Nierop et al. submitted), postural stability (van Nierop et al. 2013;

van Nierop et al. submitted) and cognitive abilities (van Nierop et al. 2014; van Nierop et al. 2012) since there is a direct connection from vestibular nuclei to eye muscles, spinal cord and higher cortical areas in the brain (Angelaki et al. 2008).

It might be plausible that a high vestibular responsiveness is positively correlated to magnetic field induced effects since patients lacking labyrinth functions do not develop a nystagmus when exposed to magnetic fields of an MRI scanner (Roberts et al. 2011) and are known to be less prone to motion sickness (Nachum et al. 2002). So far, responsiveness of the vestibular system has not been related to behavioral or cognitive test performance when exposed to MRI-related SMF. An association was shown between test performance and external stimulation of the horizontal canals by galvanic vestibular stimulation (GVS). In these experiments GVS has shown to negatively affect oculomotor functions (Aw et al. 2006; Severac Cauquil et al. 2003), postural stability (Wardman et al. 2003) and cognitive performance (see review (Utz et al. 2010)). From healthy subjects undergoing GVS, it is known that they often experience a larger variation of sensations that resemble those of an upcoming motion-sickness (Balter et al. 2004a; Balter et al. 2004b; Balter et al. 2004c; Denise et al. 1996; Mallinson et al. 2002).

The above mentioned theory suggests that strong magnetic fields might interact with the endolymph fluid of the vestibular system and that some subjects seem to respond stronger than others when (moving) in the (stray) magnetic fields of an MRI system. Therefore, we set out to investigate whether and how inter-individual differences in responsiveness of the vestibular system may modify acute effects of such magnetic fields on oculomotor functions, postural stability and cognitive performance. We selected different measures of vestibular responsiveness, as it was unknown *a priori* which measure of responsiveness would be relevant in terms of modifying acute effects of magnetic fields (e.g. responsiveness to low and medium-frequency movement, and vestibular asymmetry between left and right side).

7.2 METHODS

Subjects

A total of 36 healthy volunteers participated in the experiment (6 men and 30 women) with an average age of 22 ± SD 2.74 years (range between 18 and 30 years) recruited with flyers on bulletin boards at Utrecht University. Subjects were asked to abstain from consuming alcohol 24 hours and caffeine 3 hours before the experiment. The study was approved by the local medical ethics research committee of the University Medical Center Utrecht (UMCU), the Netherlands.

Experimental design

The experimental study (van Nierop et al. submitted; van Nierop et al. 2014) used a double-blind randomized sham-controlled crossover design in which each volunteer underwent a training session, followed by four experimental sessions of about 30 minutes each, on two consecutive days. There were two exposure conditions in the stray fields of a passively shielded 7.0 T Philips Achieva research system located at University Medical Center Utrecht, where the subject sat on a chair that was fixed to ground with their back towards the bore of the MRI magnet. In one condition, subjects were exposed to 1.0 T SMF only ('SMF') and in the other condition they were exposed to a combination of 1.0 T SMF and 2.4 T/sec TVMF ('SMF+TVMF'). TVMF were induced by standardized head movements before every single test covering an angle of 180 degrees in 0.8 s, ten movements in vertical and then ten in the horizontal plane. The start of each movement was indicated by an auditory cue. Two corresponding unexposed sham conditions were applied (<25mT) in a separate room in which an audiotape mimicked the background noise of an MRI system: one without ('sham') and one with similar standardized head movements ('sham+HM') before every single test.

Outcome measures: Cognitive tasks, oculomotor functions and postural stability

We selected outcomes measures which were previously shown to be statically significantly affected by exposure to SMF and TVMF and measures that reflect vestibular functioning. Tests which showed a significant effect of exposure were the Rivermead Behavioural Memory Test (RBMT (Wilson et al. 1989)) to assess verbal memory by recall of a short news article read out by the test leader and oculomotor functions as tested by electro-oculography recording of saccadic eye velocity. Tests on

which we found no main statistically significant effect of exposure to magnetic fields included a Romberg tasks assessing postural stability, a line bisection task for spatial orientation and oculomotor functions of smooth pursuit eye movements and saccadic accuracy and latency. Nevertheless, these tasks are related to vestibular functions and were thus included in this analysis of modifying effects of vestibular responsiveness.

Responsiveness of the vestibular organ

Vestibular responsiveness has been defined in several ways in clinical practice. Since it is unknown what kind of vestibular responsiveness would be relevant for understanding effects of exposure to magnetic fields, responsiveness of the vestibular organ (assumed to be reflected in total responsiveness of the vestibular system) of each subject was defined by three different assessment methods:

1) **MSSQ**; Subjective sensitivity to motion sickness was defined by a short version of the motion sickness susceptibility questionnaire (MSSQ (Golding 1998)), completed before the experiment.

On a separate visit after completion of the experimental sessions, vestibulo-ocular reflex amplitude strength was defined during stimulation of the horizontal canals of the vestibular organ by two different methods:

2) **Caloric Reflex**; Responsiveness to low-frequency movements around 0.003 Hz (according to Fitzgerald and Hallpike (Fitzgerald 1942)) was tested by use of the caloric test. During this test the subject lies in supine position with the head 30 degrees in flexion. A temperature gradient is created in each ear by irrigating the ear with 300 ml water of 7 degrees below and above body temperature (resp. 30 and 44 degrees Celsius) during 30 seconds. Recording of eye movements in total darkness are made by electronystagmography. Slow phase velocities were detected to calculate total caloric response by adding up the responses to cold and warm water irrigation for each labyrinth, right or left, separately. The **Unilateral weakness** of the horizontal canals of the labyrinth (or asymmetry) was defined by the difference between the caloric response to irrigation of the right and left canal according to the standard Jongkees formula (contrast function) (Furman et al. 1993).
3) **Rotary chair**; Responsiveness to medium-frequency movements was tested by the rotary chair torsion swing test. The subject is seated in a rotary chair

in total darkness with the head 30 degrees in flexion. The chair is rotating in the horizontal plane with a cosine profile around an earth vertical axis at 0.1 Hz and a peak velocity of 60°/s for about 100 seconds. Recording of eye movements are made by electronystagmography and eye velocities were detected after elimination of fast phases by median filtering. Gain and phase of the induced vestibulo-ocular reflex were estimated by Fourier analysis.

Classification of the groups according to vestibular responsiveness

For each of the different vestibular assessment methods subjects were classified in subgroups with either a normal or a high responsive vestibular system. The 'normal' and 'high' responsive groups were defined by 0-75% lowest and 75-100% highest responsive subjects, respectively.

Data analysis

The effect of exposure to magnetic fields on test performance was analyzed using linear mixed effects models. Marginal mean test performance for the normal and high responsive group was estimated for each of the conditions (sham, SMF, sham+HM, SMF+TVMF) and adjusted for practice effect and sex. Subjects were included as random effects using heterogeneous compound symmetry that assumes similar correlation between residuals of the same subject but no correlation between different subjects.

$$\text{Marginal mean} = \text{Intercept} + \beta_{\text{exposure condition}} + \beta_{\text{vestibular responsiveness by method}} + \sum\beta_{\text{exposure condition}} * \beta_{\text{vestibular responsiveness by method}} + 0.25*(\sum\beta_{\text{Session14}}) + (0.17*\beta_{\text{male}} + 0.83*\beta_{\text{female}})$$

The mixed model analysis was performed in IBM SPSS Statistics 20.0. A pair wise comparison of the estimated test results for the two exposure conditions with their respective sham conditions (SMF versus sham and SMF+TVMF versus sham+HM), was performed. Data of the postural stability task were recalculated per second in order to compare properly across tasks with different duration and to improve fit of the linear mixed models, data were log(10)transformed before statistical modelling. Statistical significance level was defined as $p<0.05$.

7.3 RESULTS

As expected, the measured responsiveness for low and medium-frequencies and unilateral weakness of the horizontal canals, as measured by the caloric reflex test and torsion swing test, were within normal and non-clinical range for all subjects, see table 1 (Carpenter 1991). Correlation between the methods defining vestibular responsiveness was very low with Pearson correlation (N=72) between MSSQ and: Caloric (-0.001, p=0.995), Rotary chair (0.294, p=0.082), Unilateral weakness (-0.270, p=0.112); between Caloric and: Rotary chair (0.067, p=0.697), Unilateral weakness (-0.281, p=0.097); between Rotary chair and Unilateral weakness (-0.055, p=0.750). Only 14 subjects were classified into the normal response group based on all four assessment methods, while none of the subjects was classified into the high responsive group based on all four assessment methods, see table 1.

Results of the mixed effects models for normal and high responsive groups are shown in table 2, 3 and 4, for oculomotor functions, postural stability and cognitive performance respectively. Table 2 A-E shows that the earlier found effects of exposure to SMF and the combination of SMF+TVMF on oculomotor functions as tested by saccadic velocity (both $p<0.001$) were not modified by vestibular responsiveness. For all vestibular responsiveness groups a (borderline) significantly increased eye velocity was found when exposed to either SMF alone or the combination of SMF and TVMF. Although some vestibular responsiveness measures show a significant change between exposure and sham condition on endpoints of saccadic accuracy, latency, pursuit gain and pursuit phase, no meaningful coherent statistically significant interactions with magnetic field exposure could be detected (interaction effects not shown).

For postural stability a (borderline) significant interaction was shown between unilateral weakness and exposure to SMF+TVMF (interaction effects not shown). Effect estimates revealed a significant improved postural stability due to exposure for subjects with high unilateral weakness in the parallel task 30 sec. ($p=0.01$), 90 sec. ($p<0.01$) and the tandem task ($p=0.05$), see table 3A-C. The other vestibular responsiveness measures did not show a consistent interaction with the outcomes for the three levels of the balance task.

Effects on cognitive functions of verbal memory and spatial orientation were not modified by vestibular responsiveness when exposed to magnetic fields, see table 4.

Table 1 Individual vestibular responsiveness based on different assessment methods. Categorization of subjects into subgroups was based on the 75th percentile, i.e. the lowest 75% were considered normal and highest 25% as high responsive (bold numbers). Lower part of table shows the categorization of subjects according to vestibular responsiveness for different assessment methods.

Subject ID		MSSQ[1]	Caloric reflex[2]	Rotary chair[3]	Unilateral weakness[4]
1		4	88	35	4.5
2		3	118	30	-10.2
3		**9**	81	46	**-13.6**
4		5	**188**	**55**	-10.6
5		5	31	**50**	-3.2
6		5	**143**	**50**	**-17.5**
7		5	**161**	**50**	8.1
8		**6**	111	**50**	6.3
9		5	**161**	40	-11.8
10		5	**159**	**50**	**-14.5**
11		3	58	**50**	**31.0**
12		4	87	40	**-35.6**
13		**6**	**153**	45	-5.9
14		4	90	30	2.2
15		4	97	35	9.3
16		5	108	**60**	-11.1
17		**7**	**138**	35	**-15.9**
18		5	107	27	-8.4
19		3	137	40	-10.9
20		4	121	35	4.1
21		3	113	40	0.9
22		**7**	80	**55**	**-15.0**
23		**6**	70	43	11.4
24		5	**170**	45	**-23.5**
25		4	71	**50**	-4.2
26		3	80	45	0.0
27		5	96	40	4.2
28		3	80	40	-10.0
29		4	97	45	**19.6**
30		3	87	35	-3.4
31		**6**	81	35	-6.2
32		**8**	90	**55**	-11.1
33		3	120	40	0.0
34		3	135	45	-8.1
35		**6**	**187**	45	-0.5
36		3	95	**50**	-9.5
Normal group	N	27	27	24	27
	Cutoff	<6	<138°	<50°	<13%
High group	N	9	9	12	9
	cutoff	≥6	≥138°	≥50°	≥13%

[1] MSSQ score on a Likert-scale ranging from 3 (no) till 12 (very high) vulnerability to motion sickness
[2] Caloric reflex is defined as the total response sum score of warm-left (WL), warm-right (WR), cold-left (CL) and cold-right (CR) reflex in degrees of slow phase nystagmus
[3] Rotary chair torsion swing test is expressed in degrees of slow phase nystagmus
[4] Unilateral weakness in percent defined by (CR+WR-CL-WL)/Total response
Pearson correlation between MSSQ and Caloric (-0.001, p=0.995); Rotary chair (0.294, p=0.082) Unilateral weakness (-0.270, p=0.112). Correlation between Caloric and Rotary chair (0.067, p=0.697); Unilateral weakness (-0.281, p=0.097). Correlation between rotary chair and Unilateral weakness (-0.055, p=0.750)

Table 2 (on next pages) Estimated test performance (and 95% Confidence intervals) for oculomotor functions of A) Saccadic velocity B) Saccadic accuracy, C) Saccadic Latency, D) Smooth pursuit gain, and E) Smooth pursuit phase. Estimates were based on an adjusted mixed model analysis of previous experiment (van Nierop et al. submitted), with classified groups in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF). The total group (N=36) in the main analysis and groups classified based on responsiveness of the vestibular organ based on: self-reported sensitivity to motion sickness (MSSQ), caloric reflex, rotary chair and unilateral weakness. Bold values are significant different between sham and exposure condition at $p<0.05$.

A Saccadic velocity to the right side[1] in degrees per second

		Condition	Estimate	CI lower	CI higher	P-value[3]
Main analysis [2]		Sham	396.93	381.74	412.13	
		SMF	440.96	425.58	456.34	**<0.01**
		Sham+HM	404.29	389.11	419.47	
		SMF+TVMF	435.68	420.09	451.27	**<0.01**
MSSQ	Normal response	Sham	397.12	379.87	414.37	
		SMF	445.93	428.51	463.35	**<0.01**
		Sham+HM	411.15	393.89	428.41	
		SMF+TVMF	430.55	412.69	448.40	**0.05**
	High response	Sham	401.50	373.12	429.89	
		SMF	422.52	392.76	452.27	0.21
		Sham+HM	386.95	358.89	415.01	
		SMF+TVMF	444.57	415.95	473.19	**<0.01**
Caloric reflex	Normal response	Sham	402.52	385.28	419.75	
		SMF	444.95	427.34	462.55	**<0.01**
		Sham+HM	408.01	390.71	425.31	
		SMF+TVMF	428.86	411.15	446.56	**0.04**
	High response	Sham	384.76	355.94	413.59	
		SMF	428.88	399.82	457.93	**0.01**
		Sham+HM	392.63	364.26	420.99	
		SMF+TVMF	450.00	419.53	480.47	**<0.01**
Rotary torsion swing test	Normal response	Sham	397.20	378.85	415.55	
		SMF	435.97	417.16	454.77	**<0.01**
		Sham+HM	399.53	380.87	418.20	
		SMF+TVMF	432.90	414.15	451.66	**<0.01**
	High response	Sham	399.20	373.72	424.68	
		SMF	450.46	424.97	475.95	**<0.01**
		Sham+HM	413.14	388.72	437.56	
		SMF+TVMF	438.52	411.30	465.74	0.10
Unilateral weakness	Normal response	Sham	393.22	375.61	410.83	
		SMF	439.83	422.21	457.45	**<0.01**
		Sham+HM	404.10	386.48	421.72	
		SMF+TVMF	434.50	416.59	452.40	**<0.01**
	High response	Sham	408.77	380.76	436.79	
		SMF	445.18	414.12	476.24	**0.04**
		Sham+HM	405.36	377.09	433.63	
		SMF+TVMF	436.59	404.87	468.30	0.08

[1] Saccadic velocity to the left side showed comparable results (data not shown)
[2] As analyzed in original experimental study (van Nierop et al. submitted)
[3] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

B. Saccadic Accuracy to the right side[1] in percent

		Condition	Estimate	CI lower	CI higher	P-value[3]
Main analysis [2]		Sham	94.72	93.27	96.17	
		SMF	94.52	93.06	95.98	0.82
		Sham+HM	94.69	93.25	96.14	
		SMF+TVMF	95.26	93.76	96.76	0.54
MSSQ	Normal response	Sham	94.36	92.69	96.03	
		SMF	95.30	93.61	96.99	0.37
		Sham+HM	94.80	93.12	96.47	
		SMF+TVMF	95.81	94.05	97.57	0.35
	High response	Sham	96.07	93.16	98.98	
		SMF	92.40	89.48	95.32	**0.05**
		Sham+HM	94.06	91.21	96.92	
		SMF+TVMF	93.55	90.68	96.42	0.78
Caloric reflex	Normal response	Sham	94.76	93.05	96.47	
		SMF	94.94	93.23	96.64	0.87
		Sham+HM	94.27	92.59	95.95	
		SMF+TVMF	95.51	93.72	97.30	0.26
	High response	Sham	94.71	91.91	97.51	
		SMF	93.64	90.64	96.65	0.56
		Sham+HM	95.67	92.63	98.72	
		SMF+TVMF	94.37	91.50	97.24	0.49
Rotary torsion swing test	Normal response	Sham	94.90	93.11	96.68	
		SMF	93.75	91.92	95.57	0.31
		Sham+HM	94.50	92.68	96.31	
		SMF+TVMF	95.26	93.36	97.16	0.52
	High response	Sham	94.43	91.83	97.03	
		SMF	96.11	93.57	98.64	0.30
		Sham+HM	95.00	92.51	97.49	
		SMF+TVMF	95.12	92.52	97.72	0.94
Unilateral weakness	Normal response	Sham	94.45	92.74	96.15	
		SMF	94.78	93.07	96.49	0.75
		Sham+HM	94.84	93.13	96.55	
		SMF+TVMF	95.66	93.84	97.47	0.46
	High response	Sham	95.79	92.82	98.77	
		SMF	93.60	90.42	96.78	0.26
		Sham+HM	94.13	91.21	97.04	
		SMF+TVMF	94.09	91.20	96.97	0.98

[1] Saccadic accuracy to the left side showed comparable results (data not shown)

[2] As analyzed in original experimental study (van Nierop et al. submitted)

[3] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

C. Saccadic Latency in milliseconds

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	108.91	107.28	110.54	
		SMF	109.22	107.56	110.88	0.76
		Sham+HM	108.64	107.01	110.27	
		SMF+TVMF	108.99	107.26	110.73	0.73
MSSQ	Normal response	Sham	109.63	107.91	111.35	
		SMF	110.43	108.72	112.14	0.42
		Sham+HM	109.08	107.34	110.82	
		SMF+TVMF	110.20	108.25	112.14	0.33
	High response	Sham	107.48	104.67	110.28	
		SMF	105.13	101.98	108.29	0.23
		Sham+HM	107.06	104.48	109.65	
		SMF+TVMF	105.89	103.33	108.45	0.47
Caloric reflex	Normal response	Sham	108.94	107.08	110.81	
		SMF	109.16	107.22	111.09	0.86
		Sham+HM	109.28	107.41	111.15	
		SMF+TVMF	108.15	106.20	110.11	0.34
	High response	Sham	108.72	105.71	111.72	
		SMF	109.55	106.69	112.42	0.65
		Sham+HM	106.59	103.58	109.60	
		SMF+TVMF	111.09	107.54	114.64	**0.04**
Rotary torsion swing test	Normal response	Sham	108.90	107.02	110.78	
		SMF	110.31	108.30	112.33	0.24
		Sham+HM	108.10	106.09	110.11	
		SMF+TVMF	108.56	106.55	110.56	0.72
	High response	Sham	109.35	106.58	112.12	
		SMF	108.03	105.57	110.49	0.43
		Sham+HM	109.17	106.80	111.53	
		SMF+TVMF	108.86	105.75	111.96	0.87
Unilateral weakness	Normal response	Sham	108.46	106.59	110.34	
		SMF	108.99	107.11	110.86	0.65
		Sham+HM	108.49	106.62	110.37	
		SMF+TVMF	109.00	107.03	110.98	0.67
	High response	Sham	110.40	107.54	113.26	
		SMF	110.79	107.56	114.01	0.84
		Sham+HM	108.93	106.00	111.86	
		SMF+TVMF	108.01	104.68	111.35	0.65

[1] As analyzed in original experimental study (van Nierop et al. submitted)
[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

D. Pursuit gain in percent

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	89.48	88.01	90.96	
		SMF	90.29	88.79	91.79	0.37
		Sham+HM	88.98	87.51	90.46	
		SMF+TVMF	90.20	88.69	91.70	0.18
MSSQ	Normal response	Sham	90.02	88.37	91.66	
		SMF	91.07	89.38	92.76	0.33
		Sham+HM	89.64	88.00	91.28	
		SMF+TVMF	90.95	89.26	92.64	0.22
	High response	Sham	87.96	85.15	90.77	
		SMF	87.99	85.18	90.80	0.99
		Sham+HM	86.98	84.12	89.85	
		SMF+TVMF	88.08	85.18	90.98	0.55
Caloric reflex	Normal response	Sham	89.55	87.88	91.23	
		SMF	89.47	87.75	91.19	0.94
		Sham+HM	88.46	86.77	90.15	
		SMF+TVMF	90.08	88.35	91.82	0.13
	High response	Sham	89.23	86.26	92.19	
		SMF	92.56	89.62	95.51	0.07
		Sham+HM	90.50	87.63	93.37	
		SMF+TVMF	90.72	87.79	93.64	0.90
Rotary torsion swing test	Normal response	Sham	89.56	87.75	91.36	
		SMF	90.09	88.24	91.94	0.64
		Sham+HM	88.15	86.36	89.94	
		SMF+TVMF	90.15	88.29	92.02	0.08
	High response	Sham	89.26	86.72	91.79	
		SMF	90.69	88.12	93.26	0.36
		Sham+HM	90.70	88.11	93.29	
		SMF+TVMF	90.29	87.73	92.84	0.80
Unilateral weakness	Normal response	Sham	88.81	87.12	90.49	
		SMF	89.64	87.89	91.38	0.43
		Sham+HM	88.97	87.28	90.65	
		SMF+TVMF	90.28	88.54	92.01	0.21
	High response	Sham	91.69	88.77	94.61	
		SMF	91.82	88.93	94.71	0.94
		Sham+HM	89.11	86.15	92.05	
		SMF+TVMF	90.17	87.10	93.25	0.56

[1] As analyzed in original experimental study (van Nierop et al. submitted)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

E. Pursuit Phase in degrees

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	-2.36	-3.28	-1.43	
		SMF	-2.48	-3.42	-1.54	0.84
		Sham+HM	-2.52	-3.45	-1.60	
		SMF+TVMF	-1.48	-2.42	-0.54	0.09
MSSQ	Normal response	Sham	-2.44	-3.49	-1.38	
		SMF	-2.82	-3.89	-1.74	0.58
		Sham+HM	-2.30	-3.35	-1.25	
		SMF+TVMF	-2.16	-3.24	-1.09	0.85
	High response	Sham	-2.08	-3.91	-0.25	
		SMF	-1.07	-2.89	0.76	0.39
		Sham+HM	-3.27	-5.10	-1.44	
		SMF+TVMF	0.08	-1.74	1.90	**0.01**
Caloric reflex	Normal response	Sham	-2.15	-3.22	-1.07	
		SMF	-2.26	-3.36	-1.16	0.87
		Sham+HM	-2.57	-3.65	-1.50	
		SMF+TVMF	-1.57	-2.67	-0.47	0.16
	High response	Sham	-3.03	-4.90	-1.17	
		SMF	-3.03	-4.91	-1.14	1.00
		Sham+HM	-2.42	-4.30	-0.54	
		SMF+TVMF	-1.20	-3.08	0.68	0.32
Rotary torsion swing test	Normal response	Sham	-2.04	-3.18	-0.90	
		SMF	-2.22	-3.38	-1.05	0.82
		Sham+HM	-2.35	-3.49	-1.21	
		SMF+TVMF	-1.16	-2.32	0.00	0.12
	High response	Sham	-2.98	-4.61	-1.36	
		SMF	-3.00	-4.62	-1.38	0.99
		Sham+HM	-2.86	-4.47	-1.25	
		SMF+TVMF	-2.09	-3.73	-0.45	0.48
Unilateral weakness	Normal response	Sham	-2.26	-3.32	-1.20	
		SMF	-3.23	-4.31	-2.15	0.16
		Sham+HM	-2.52	-3.58	-1.46	
		SMF+TVMF	-1.03	-2.11	0.04	**0.03**
	High response	Sham	-2.55	-4.37	-0.74	
		SMF	-0.68	-2.57	1.20	0.11
		Sham+HM	-2.43	-4.25	-0.60	
		SMF+TVMF	-2.55	-4.45	-0.65	0.92

[1] As analyzed in original experimental study (van Nierop et al. submitted)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

Table 3 (on next pages) Estimated test performance (and 95% Confidence intervals) for postural stability in A) Tandem task for 30 seconds B) Tandem task for 90 seconds, and C) Parallel task for 30 seconds. Estimates were based on an adjusted mixed model analysis of previous experiment (van Nierop et al. submitted), with classified groups in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF). The total group (N=36) in the main analysis and groups classified based on responsiveness of the vestibular organ based on: self-reported sensitivity to motion sickness (MSSQ), caloric reflex, rotary chair and unilateral weakness. Bold values are significant different between sham and exposure condition at $p<0.05$.

A. Postural stability with feet 30 sec. in parallel position sway path in mm/s (based on back transformed results of an analysis with log10 transformation)

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	6.71	5.20	8.67	
		SMF	8.34	6.46	10.77	0.25
		Sham+HM	9.66	7.48	12.47	
		SMF+TVMF	6.85	5.31	8.86	0.07
MSSQ	Normal response	Sham	6.92	5.13	9.32	
		SMF	7.91	5.87	10.66	0.54
		Sham+HM	9.59	7.11	12.92	
		SMF+TVMF	7.13	5.30	9.61	0.18
	High response	Sham	6.32	3.78	10.57	
		SMF	10.00	5.94	16.82	0.23
		Sham+HM	9.89	5.90	16.54	
		SMF+TVMF	5.79	3.43	9.77	0.16
Caloric reflex	Normal response	Sham	5.94	4.44	7.94	
		SMF	7.83	5.85	10.50	0.20
		Sham+HM	9.77	7.30	13.09	
		SMF+TVMF	5.93	4.42	7.94	**0.02**
	High response	Sham	10.47	6.30	17.38	
		SMF	9.95	5.92	16.72	0.89
		Sham+HM	9.20	5.59	15.14	
		SMF+TVMF	10.09	6.07	16.76	0.81
Rotary torsion swing test	Normal response	Sham	5.90	4.31	8.10	
		SMF	8.53	6.24	11.64	0.12
		Sham+HM	8.39	6.13	11.47	
		SMF+TVMF	6.97	5.10	9.54	0.43
	High response	Sham	8.81	5.71	13.58	
		SMF	7.85	4.97	12.40	0.73
		Sham+HM	12.62	8.13	19.64	
		SMF+TVMF	6.75	4.30	10.56	0.06
Unilateral weakness	Normal response	Sham	6.87	5.12	9.22	
		SMF	8.05	6.01	10.80	0.46
		Sham+HM	8.15	6.07	10.93	
		SMF+TVMF	7.40	5.51	9.91	0.65
	High response	Sham	6.41	3.90	10.56	
		SMF	9.38	5.52	15.95	0.31
		Sham+HM	15.56	9.46	25.59	
		SMF+TVMF	5.48	3.23	9.32	**0.01**

[1] As analyzed in original experimental study (van Nierop et al. submitted)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

B. Postural stability with feet 90 sec. in parallel position sway path in mm/s (based on back transformed results of an analysis with log(10) transformation)

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	6.37	4.95	8.18	
		SMF	6.34	4.94	8.15	0.99
		Sham+HM	7.87	6.13	10.12	
		SMF+TVMF	5.13	3.99	6.60	**0.01**
MSSQ	Normal response	Sham	6.41	4.81	8.54	
		SMF	5.94	4.46	7.91	0.69
		Sham+HM	8.87	6.65	11.83	
		SMF+TVMF	4.90	3.67	6.54	**<0.01**
	High response	Sham	6.15	3.74	10.14	
		SMF	7.83	4.72	12.97	0.48
		Sham+HM	5.48	3.35	8.96	
		SMF+TVMF	5.90	3.59	9.70	0.82
Caloric reflex	Normal response	Sham	6.05	4.53	8.09	
		SMF	6.04	4.52	8.06	0.99
		Sham+HM	7.18	5.39	9.58	
		SMF+TVMF	4.89	3.65	6.54	**0.05**
	High response	Sham	7.24	4.45	11.81	
		SMF	7.53	4.51	12.54	0.91
		Sham+HM	10.57	6.33	17.67	
		SMF+TVMF	5.82	3.53	9.60	0.09
Rotary torsion swing test	Normal response	Sham	5.66	4.16	7.70	
		SMF	5.86	4.31	7.95	0.87
		Sham+HM	7.80	5.73	10.61	
		SMF+TVMF	5.05	3.69	6.90	**0.04**
	High response	Sham	8.04	5.20	12.43	
		SMF	7.46	4.78	11.67	0.81
		Sham+HM	7.98	5.16	12.31	
		SMF+TVMF	5.33	3.45	8.26	0.18
Unilateral weakness	Normal response	Sham	6.89	5.17	9.16	
		SMF	5.87	4.43	7.80	0.41
		Sham+HM	6.79	5.10	9.06	
		SMF+TVMF	5.41	4.04	7.24	0.24
	High response	Sham	5.02	3.06	8.28	
		SMF	8.13	4.77	13.86	0.17
		Sham+HM	11.72	7.20	19.11	
		SMF+TVMF	4.49	2.76	7.31	**<0.01**

[1] As analyzed in original experimental study (van Nierop et al. submitted)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

C. Postural stability with feet in tandem position sway path in mm/s (based on back transformed results of an analysis with log(10) transformation)

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	21.53	15.58	29.74	
		SMF	23.28	16.87	32.18	0.72
		Sham+HM	26.98	19.51	37.23	
		SMF+TVMF	28.51	20.61	39.41	0.80
MSSQ	Normal response	Sham	23.07	15.80	33.66	
		SMF	23.17	15.89	33.74	0.99
		Sham+HM	28.77	19.71	42.07	
		SMF+TVMF	29.99	20.50	43.78	0.88
	High response	Sham	17.82	9.26	34.32	
		SMF	23.99	12.35	46.54	0.51
		Sham+HM	21.53	11.25	41.13	
		SMF+TVMF	24.49	12.69	47.20	0.77
Caloric reflex	Normal response	Sham	19.32	13.27	28.11	
		SMF	23.01	15.86	33.45	0.49
		Sham+HM	27.29	18.81	39.63	
		SMF+TVMF	34.12	23.40	49.76	0.38
	High response	Sham	29.85	15.82	56.24	
		SMF	24.32	12.52	47.28	0.65
		Sham+HM	25.41	13.21	48.91	
		SMF+TVMF	16.75	8.75	32.05	0.35
Rotary torsion swing test	Normal response	Sham	17.42	11.72	25.88	
		SMF	21.93	14.82	32.51	0.39
		Sham+HM	26.55	17.85	39.46	
		SMF+TVMF	34.20	22.93	51.05	0.35
	High response	Sham	32.36	18.55	56.53	
		SMF	26.00	14.68	46.17	0.57
		Sham+HM	28.25	16.22	49.16	
		SMF+TVMF	19.91	11.32	35.02	0.36
Unilateral weakness	Normal response	Sham	19.54	13.48	28.29	
		SMF	20.99	14.55	30.30	0.77
		Sham+HM	23.71	16.34	34.37	
		SMF+TVMF	35.24	24.19	51.40	0.12
	High response	Sham	27.93	14.74	52.99	
		SMF	32.14	16.09	64.10	0.76
		Sham+HM	37.58	20.02	70.58	
		SMF+TVMF	16.18	8.56	30.65	**0.05**

[1] As analyzed in original experimental study (van Nierop et al. submitted)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

Table 4 (on next pages) Estimated test performance (and 95% Confidence intervals) on cognitive performance on A) verbal memory B) spatial orientation. Estimates were based on an adjusted mixed model analysis of previous experiment (van Nierop et al. submitted), with classified groups in the sham condition, static magnetic field condition (SMF), sham condition with additional head movements (sham+HM) and the static magnetic field condition with additional time-varying magnetic fields induced by head movements (SMF+TVMF). The total group (N=36) in the main analysis and groups classified based on responsiveness of the vestibular organ based on: self-reported sensitivity to motion sickness (MSSQ), caloric reflex, rotary chair and unilateral weakness. Bold values are significant different between sham and exposure condition at $p<0.05$.

A. RBMT verbal memory delayed recall in correct recalled words

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	9.80	8.62	10.97	
		SMF	10.56	9.38	11.74	0.18
		Sham+HM	10.56	9.38	11.73	
		SMF+TVMF	9.37	8.19	10.54	**0.04**
MSSQ	Normal response	Sham	8.59	7.27	9.91	
		SMF	9.99	8.68	11.30	**0.03**
		Sham+HM	9.69	8.36	11.02	
		SMF+TVMF	8.82	7.48	10.15	0.17
	High response	Sham	13.34	11.10	15.58	
		SMF	12.09	9.79	14.38	0.27
		Sham+HM	12.96	10.80	15.12	
		SMF+TVMF	11.47	9.31	13.63	0.16
Caloric reflex	Normal response	Sham	9.74	8.31	11.17	
		SMF	10.50	9.07	11.93	0.26
		Sham+HM	10.64	9.22	12.07	
		SMF+TVMF	9.52	8.09	10.94	0.09
	High response	Sham	9.79	7.42	12.15	
		SMF	10.59	8.19	12.99	0.48
		Sham+HM	10.51	8.03	12.99	
		SMF+TVMF	9.02	6.54	11.51	0.21
Rotary torsion swing test	Normal response	Sham	9.47	8.03	10.91	
		SMF	9.55	8.09	11.02	0.91
		Sham+HM	10.13	8.66	11.60	
		SMF+TVMF	8.62	7.17	10.06	**0.03**
	High response	Sham	10.28	8.19	12.37	
		SMF	12.37	10.38	14.37	**0.04**
		Sham+HM	11.56	9.59	13.54	
		SMF+TVMF	11.07	8.96	13.18	0.62
Unilateral weakness	Normal response	Sham	9.87	8.44	11.30	
		SMF	10.31	8.89	11.73	0.50
		Sham+HM	10.50	9.07	11.93	
		SMF+TVMF	9.10	7.66	10.54	**0.04**
	High response	Sham	9.37	6.94	11.81	
		SMF	11.25	8.68	13.82	0.11
		Sham+HM	10.91	8.49	13.33	
		SMF+TVMF	10.25	7.83	12.66	0.55

[1] As analyzed in original experimental study (van Nierop et al. 2014)
[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

B. Line Bisection in percent deviation from the middle of the line (100)

		Condition	Estimate	CI lower	CI higher	P-value[2]
Main analysis [1]		Sham	100.11	99.51	100.70	
		SMF	99.82	99.22	100.41	0.38
		Sham+HM	99.73	99.13	100.33	
		SMF+TVMF	99.44	98.85	100.04	0.39
MSSQ	Normal response	Sham	100.15	99.51	100.80	
		SMF	99.73	99.08	100.38	0.26
		Sham+HM	99.59	98.94	100.24	
		SMF+TVMF	99.41	98.77	100.06	0.64
	High response	Sham	100.17	99.07	101.26	
		SMF	100.28	99.18	101.37	0.87
		Sham+HM	100.31	99.22	101.40	
		SMF+TVMF	99.71	98.61	100.80	0.36
Caloric reflex	Normal response	Sham	99.91	99.16	100.65	
		SMF	99.61	98.87	100.36	0.45
		Sham+HM	99.47	98.73	100.21	
		SMF+TVMF	99.39	98.65	100.14	0.84
	High response	Sham	100.37	99.38	101.37	
		SMF	100.08	99.06	101.10	0.67
		Sham+HM	100.18	99.17	101.19	
		SMF+TVMF	99.29	98.29	100.29	0.18
Rotary torsion swing test	Normal response	Sham	99.72	99.05	100.39	
		SMF	99.64	98.97	100.31	0.83
		Sham+HM	99.15	98.48	99.82	
		SMF+TVMF	98.95	98.28	99.63	0.61
	High response	Sham	101.06	100.02	102.11	
		SMF	100.16	99.09	101.24	0.18
		Sham+HM	101.23	100.19	102.26	
		SMF+TVMF	100.64	99.59	101.68	0.37
Unilateral weakness	Normal response	Sham	100.22	99.50	100.94	
		SMF	100.33	99.60	101.05	0.79
		Sham+HM	100.09	99.37	100.81	
		SMF+TVMF	99.61	98.89	100.34	0.25
	High response	Sham	100.11	99.20	101.01	
		SMF	99.00	98.08	99.91	0.06
		Sham+HM	99.22	98.31	100.12	
		SMF+TVMF	99.31	98.40	100.21	0.88

[1] As analyzed in original experimental study (van Nierop et al. 2014)

[2] p-value of sham versus SMF condition and sham+HM versus SMF+TVMF condition

7.4 DISCUSSION

It has been hypothesized that exposure to strong magnetic fields affect the vestibular system and that this might explain some of the acute effects shown previously. We aimed to assess whether measures of responsiveness of the vestibular system based on self-reports and well-known clinical vestibular tests, modify the effect of MRI-related magnetic stray fields on oculomotor, postural stability and cognitive functions in healthy subjects. The main analysis, showed effects of (movement) in the stray SMF of an MRI scanner on saccadic velocity (van Nierop et al. submitted) and verbal memory (van Nierop et al. 2014). In the current analysis postural stability showed a consistent (almost) significant interaction between unilateral weakness and exposure to SMF+TVMF in all three tasks. This indicated an improved postural stability in the SMF+TVMF condition for subjects with unilateral weakness, in the parallel task 30 sec. ($p=0.01$), parallel task 90 sec. ($p<0.01$), and tandem task ($p=0.05$). Although a few significant interactions between MSSQ and magnetic field exposure were shown for saccadic and pursuit eye movements, these were not consistent. Effects on cognitive functions when exposed to magnetic fields were not modified by vestibular responsiveness.

In this study we incorporated multiple assessment methods, each assessing different aspects of vestibular responsiveness since we did not know a priori which one of these would be important in modifying MRI-related magnetic field effects. The vestibular tests used to define vestibular responsiveness are not solely a function of the sensitivity of the vestibular labyrinth per se, but also of signal processing in the brain, learning, alertness and in case of reflexes also upon the efferent sensitivity. The current available vestibular tests showed responsiveness to the applied stimulus and to some extent reflected vestibular sensitivity as well. The tests aimed to quantify the function of a specific labyrinthine substructure (canals, utriculus and sacculus) and their associated neural tracts or pathways. As was also shown previously, the outcomes of the different vestibular tests did not correlate very well within subjects and between assessment methods measuring vestibular responsiveness or (subjective) susceptibility to motion sickness (Buyuklu et al. 2009; Furman et al. 1989). An interaction effect between a certain responsiveness measure and exposure to magnetic fields would point at a mediating role for the vestibular system in acute effects of MRI-related magnetic field exposure. However, the absence of a significant interaction does not necessarily mean that the vestibular organ is not involved in

magnetic field induced behavioral changes. In that case the role of the vestibular organ would be considered the same in all subjects regardless of vestibular responsiveness.

Postural stability was found to be diminished when performing head movements in the sham condition, in some of the created high responsive groups based on objective vestibular assessment methods. The subgroup with relatively high unilateral weakness showed most strongly and consistently postural instability over all tasks in the sham with head movements condition versus sham only condition. In subjects with unilateral weakness the left and right semicircular canals are not equally sensitive for the stimulus of head rotation, resulting in deteriorated postural stability. In contrast, performing head movements when exposed to a SMF, resulting in an additional TVMF magnetic field, postural stability improved significantly among those individuals with a high unilateral weakness, over all three levels of complexity of the task. For subjects with a normal unilateral weakness we observed an opposite effect of decreased postural stability when performing head movements within the SMF versus sham with head movements, although this did not reach statistical significance. We cannot substantiate a plausible mechanism, but one might speculate that subjects with unilateral weakness seem to use the magnetic field as an orientation frame. Furthermore, it could be argued that subjects with a relative high responsive vestibular system could either have a decreased performance (by disturbance or distraction) or an increased performance (arousal) on cognitive and vestibular related endpoints compared to subjects with a normal responsive vestibular organ when exposed to MRI-related magnetic fields.

It has been suggested that strong magnetic fields interact with the endolymph fluid of the vestibular system. This could result in improved oculomotor functions of saccadic velocity (van Nierop et al. submitted). Although several interactions between MSSQ and magnetic field were revealed none of the saccadic and pursuit outcomes were coherent or showed consistency and no interactions were found with the other responsiveness measures. Therefore we found no reliable evidence that vestibular responsiveness did not modify effects on earlier identified changes in saccadic velocity by the stray magnetic fields of the MRI scanner or other oculomotor functions.

In this study we used 36 healthy young volunteer in which vestibular responsiveness was defined after completing the experimental sessions, for logistical reasons. It would have been preferable to use vestibular responsiveness as an

inclusion criterion to create larger contrast between normal and high responsive groups among healthy volunteers and consequently assess vestibular responsiveness before the experimental sessions. Moreover, in subsequent studies it would be interesting to assess larger groups of subjects with a broader range in unilateral weakness.

This study suggests that unilateral weakness of the horizontal canals modifies acute effects of exposure to a combination of SMF and TVMF on postural performance, indicating that SMF+TVMF exposure improved balance among those with high unilateral weakness. Vestibular responsiveness as defined by MSSQ did modify some effects of exposure to SMF and SMF+TVMF on oculomotor performance but these findings were not coherent. We found no evidence that effects of magnetic field exposure on cognitive performance was modified by vestibular responsiveness. As this is the first attempt to explore the role of vestibular responsiveness, further research is needed to extend and confirm our finding.

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Chapter 8

Test performance after low-intensity galvanic vestibular stimulation compared with effects of exposure to MRI-related stray magnetic fields

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ABSTRACT

Observed changes in test performance during MRI-related magnetic field exposure are suggested to be mediated by the vestibular system. Therefore, the effects of galvanic vestibular stimulation (GVS) on test performance were compared to changes in test performance when exposed to stray static magnetic fields of an MRI scanner as shown in previous research. In a balanced randomized cross-over design 30 healthy volunteers underwent GVS (binaural bipolar sinusoidal with peak amplitude of 1.0 mA and 0.4 Hz) and 'sham' stimulation (0 mA and 0 Hz) for 20 seconds before every single task of the test battery. Vestibular ocular reflex and tasks for postural stability, oculomotor and cognitive performance were assessed. We found significant effects of GVS on attention and concentration, visuomotor performance, and visual acuity. Moreover, these effects of GVS exposure on test performance did not resemble test performance during exposure to MRI-related stray magnetic fields. Based on these findings we cannot confirm that the vestibular system plays a (mediating) role in effects of MRI-related magnetic field on test performance, nor do they allow us to exclude this possibility.

8.1 INTRODUCTION

Employees working in Magnetic Resonance Imaging (MRI) departments report sensory symptoms of nausea, dizziness and a metallic taste when exposed to the stray magnetic fields of an MRI scanner (Schaap et al. 2014; Wilen et al. 2011). The sensory symptoms have been specifically reported when moving in the stray magnetic fields (SMF) of the scanner system herewith inducing a low-frequency movement-induced time-varying magnetic field (TVMF). Postural instability (van Nierop et al. 2013) , changed oculomotor functions (van Nierop et al. submitted) and cognitive (related) changes such as decreased verbal memory (van Nierop et al. 2014), attention and concentration, visual acuity, spatial orientation, visuomotor performance, and (van Nierop et al. 2012) have also been associated with acute exposure to a combination of SMF and TVMF. It has been suggested that most of these behavioral changes are primarily due to exposure to the specific combination of SMF and movement-induced TVMF. This is because those who moved faster, resulting in higher TVMF exposure, had more sensory symptoms (de Vocht et al. 2006). Moreover, the combination of SMF and TVMF showed decreased verbal memory performance where exposure to SMF only did not (van Nierop et al. 2014). An important mediating role for the vestibular system has been suggested in evoking these sensory symptoms and possibly the changes in test performance (Glover et al. 2007; van Nierop et al. 2013; van Nierop et al. 2012). Earlier research demonstrated a magnetic field induced vestibular-ocular reflex resulting in a robust nystagmus (Roberts et al. 2011). Interestingly, these spontaneous eye movements were absent in vestibular deficit patients. To find out if the vestibular system plays a (mediating) role we compared changes in test performance as found in the stray magnetic fields of an MRI scanner with those after direct stimulation of the vestibular system i.e. by Galvanic Vestibular Stimulation (GVS). If GVS would result in a similar behavioral response pattern, this would support the hypothesis that the vestibular system plays a role in the observed acute effects of MRI-related magnetic field exposure.

Galvanic stimulation is a non-invasive technique in which electrodes with opposite polarity are applied to the skull. Different stimulation patterns, frequencies and amplitudes can be administered to target rather specific brain areas by changing their cortical excitability. Hence, to stimulate the vestibular system in GVS, the electrodes are placed retro-auricular on each mastoid. During stimulation the discharge pattern of the semicircular canal and otholith afferents are affected in the

vestibular nerve running underneath the mastoids (Goldberg et al. 1984; Graf et al. 1986; Zwergal et al. 2009). Via the nervus vestibulo-cochlearis, vestibular nuclei in the brainstem and thalamic nuclei, the parietoinsular vestibular cortex (PIVC) is activated (Fink et al. 2003; Lobel et al. 1999). Subsequently, other multisensory cortical and subcortical vestibular areas are stimulated depending on the polarity of the current (Bense et al. 2001; Bucher et al. 1998; Guldin et al. 1998; Stephan et al. 2005). GVS at certain stimulation intensities is known to induce a virtual signal of head movement in space, besides sensory symptoms of nausea, dizziness, tingling skin, taste sensations and light flashes (Fitzpatrick et al. 2004; Fitzpatrick et al. 2002; Stephan et al. 2005). These symptoms show a remarkable resemblance to those reported during movement in a stray SMF of an MRI system.

GVS is also known to cause postural changes of standing subjects to sway towards the anodal side by modulating the ongoing vestibular signals. The firing rate of the vestibular afferents on the cathodal side is increased and the firing rate on the anodal side is decreased upon stimulation (Goldberg et al. 1984; Lowenstein 1955; Wardman et al. 2003b). This results in a sway which is direction specific (Hlavacka et al. 1985; Inglis et al. 1995) and increases with higher stimulus amplitude (Coats 1973a; Day et al. 1997). Where currents below 1.0 mA mainly seem to induce postural changes, higher currents induce a static torsion of the eye and stimulation above 3 mA induces a horizontal-torsional nystagmus towards the anodal side (MacDougall et al. 2002; MacDougall et al. 2005; MacDougall et al. 2003; Schneider et al. 2002; Swaak et al. 1975; Watson et al. 1998; Zink et al. 1998; Zink et al. 1997). Spontaneous eye movements in the horizontal direction were observed when stimulated with a bipolar rectangular pulse at 0.5 mA (Aw et al. 2006; Severac Cauquil et al. 2003) Similar to the found torsion of the eye, the deviation of the subjective visual vertical was shifted towards the anodal side (Mars et al. 2005; Tardy-Gervet et al. 1998). As was subjective body orientation, haptic perception (Mars et al. 2005), spatial processing (Ferre et al. 2013b) and gaze stability during dynamic visual acuity (Moore et al. 2006). This suggests that GVS influences processes controlling spatial orientation. Other studies among healthy subjects also found that higher order cognitive functions could be affected during GVS. Stimulation with different frequencies, amplitudes and polarities resulted in a decreased performance on short-term spatial memory and egocentric mental rotation (Dilda et al. 2012), response times for visual memory (Wilkinson et al. 2008), randomness of number generation (Ferre et al. 2013c), somatosensory perception (Ferre et al. 2013d) and location of

illusory touch and hand ownership (Lopez et al. 2010). Furthermore, GVS resulted in improved response times in a mental transformation task (Lenggenhager et al. 2008) and enhanced somatosensory sensitivity (Ferre et al. 2013a). Most of these studies were performed among patients, applying supra-threshold stimulation amplitudes above 1.0 mA, with direct currents (DC).

Taken together these results show that GVS is an appropriate method to stimulate the vestibular organ directly. The adjustability and controllability of GVS make it an interesting model to compare with effects of MRI-related magnetic field exposure on behavioral test performance (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012).

8.2 METHODS

For comparison of these results with earlier performed experimental MRI studies (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012), subject population and methods were kept as similar as possible.

Subjects

A total of 30 healthy volunteers participated in the experiment (7 men and 23 women) with an average age of 21 ± SD 2.82 years (range between 18 and 28 years) recruited with flyers on bulletin boards at Utrecht University. Of the total group of responders who filled in a screenings questionnaire (n=42), the first 30 eligible subjects with similar characteristic as in the MRI experiments, were enrolled in the study based on the following exclusion criteria: history of neurological disease or epilepsy, serious vision deficiencies, use of medication (except for birth control), use of soft or hard drugs and excessive use of alcohol (>2 units per day) or coffee (>5 cups per day) and self-reported sensitivity to motion sickness in adulthood as assessed by the motion sickness questionnaire (MSSQ) (Golding 1998). Sensitivity for motion sickness was defined as a score >6 on a 12-point Likert scale.

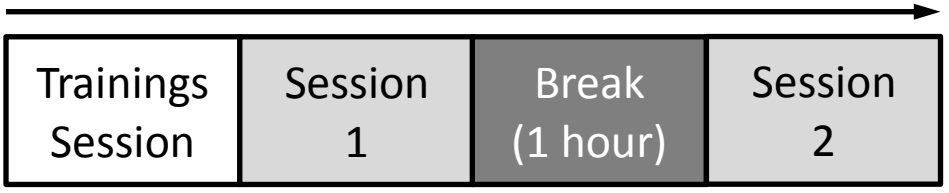
Of all participants, twenty-eight participants had acquired at least (pre-) university level education and 2 finished lower secondary professional education (VMBO). Based on a short version of the MSSQ, 10 subjects reported they never had symptoms of motion sickness at all (MSSQ score 3), 14 subjects occasionally had

symptoms (score 4 or 5) and 6 subjects had symptoms on a regular basis (score between 6 and 9). Subjects were asked to abstain from consuming alcohol 24 hours and caffeine 3 hours prior to the experiment. A modest incentive gift voucher was provided for every completed test session. The study was approved by the local medical ethics research committee of the University Medical Center Utrecht (UMCU), the Netherlands.

Experimental design

In a single blind balanced randomized cross-over design each volunteer underwent two experimental sessions of 65 minutes with an hour break in between sessions, see Figure 1. Two carbon electrodes (Uni-patch™, with 17.0 cm^2 surface) attached to a non-woven compress (Cutisoft 5x5 cm, BSN medical, Germany) were placed on each mastoid behind the ear and secured using an EEG cap. To improve conductance, a saline solution was applied by a pipet every 10 minutes. Subjects were exposed to either low intensity binaural bipolar sinusoidal galvanic vestibular stimulation with alternating current (AC) at 0.4 Hz and peak amplitude of 1.0 mA or 'sham' stimulation (0 mA and 0 Hz) for 20 seconds before every single task of the test battery. The active or sham stimulation was assigned by the test leader according to an a priori randomization scheme, and administered by a computer running Balancelab (Maastricht Instruments©).

A) Overview of experiment



B) Content of each session

Time	Task	Description	Endpoint
0'	RBMT memory task	Recall of a short story read by the test leader immediate and after a delay of 50 minutes	Correct recalled words
4'	MCG memory task	Recall of a picture shown by the test leader immediate and after a delay of 55 minutes	Correct recalled lines
7'	Letter-number sequence	Reproduce and ordering of letter and numbers in logical order	Items of longest row multiplied by amount of correct recalled rows
11'	Roadmap task	Left right orientation on a city map as fast as possible	Time (in sec) to complete task
14'	Kappers task	Haptically (blindfolded) place a bar in parallel position with a reference bar	Average deviation (in degrees) from reference bar
20'	Line bisection task	Mark the middle of 20 random aligned horizontal lines	Deviation (in percent) from true middle of the line (100%)
23'	Visual tracking task	Track 9 tangled lines on paper as fast as possible	Time to complete the task (in sec)
25'	Judgment of Line Orientation task	Judge the orientation of 2 tilted lines with reference lines as fast as possible	Amount of false judged lines
29'	Symbol Cancellation task	Cancel one target symbol out of different symbols in 60 seconds	*Speed* is calculated as correct scored items in 60 seconds.
32'	Pursuit aiming task	Place dots within small circles in 60 seconds, a version with small and large circles	*Speed* is calculated as correct scored items in 60 seconds. *Precision* is calculated as total correct responses divided by total amount of responses in 60 seconds.
35'	F.A.C.T.	Recognize the direction of lines with shrinking contrast with one blinded eye at different frequency patterns	Contrast sensitivity level in cycles per degree
40'	Letter-number sequence	As in earlier task	
43'	RBMT	Delayed recall of earlier task	

Figure 1B continued

Time	Task	Description	Endpoint
46'	MCG	Delayed recall of earlier task	
49'	Reaction time task [45,46] -Simple -Complex -Inhibition	Press target button when alights and return to home button (1 option), 30 repeats; (9 options), 30 repeats; Press target button left to the one that alights and return to home button (8 options), 30 repeats	*Reaction time* is time release of home button after stimulus. *Motion time* is time needed to go from home button to target button. *Disengagement time* is time needed to release the target button.
54'	Smooth pursuit	Fixate and track of a sinusoidal stimulus, presented at 0.2 Hz with 4.4°/s	*Gain* is the ratio of eye velocity and target velocity (in percent). *Phase* is the shift between eye and target motion as a function of frequency (in degrees per second)
57'	Saccade	Fixate and track of a stimulus, to the right, middle, left and vice versa	*Velocity* is the maximum tracking speed (in degrees per second). *Accuracy* is the ratio of actual amplitude divided by the desired amplitude (in percent) *Latency* is the delay between target and initiation of eye displacement (in msec.)
59'	Spontaneous eye movements	Fixate to an imaginary point during 20 seconds in darkness with eyes closed	Fast phase eye movements (in degree)
60'	Postural stability task	Stand with feet in parallel or tandem position, barefoot with arms alongside the body and eyes closed	Average sway *path* (in mm/s), *velocity* (in mm/s^2) and covered *area* (in mm^2/s) were calculated as sum of x-, y- and z- direction.

Figure 1 Set-up of the experiment (A). Each subject underwent a trainings session followed by 2 experimental sessions, in randomized order. Before each task sham or sinusoidal 1.0 mA GVS was applied for 20 sec during performance of head movements. The test battery in order of assessment, included tasks for cognitive functions, postural stability and oculomotor functions as specified (B).

To reduce a possible practice effect in cognitive test performance, subjects completed a full training session at least half an hour prior to the first experimental session. Before each session, subjects were asked to complete a questionnaire about current symptoms. After each session they completed a short questionnaire on symptoms during or after the session and their perception of whether or not they had been exposed to GVS.

Similar to the sham condition in the MRI studies (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012), subjects were seated inside a standardized tent (located in a regular room at the University) with the acoustic noise of an MRI cryostat pump present. To mimic the time-varying magnetic field exposure condition, standardized head movements were also employed during GVS/sham exposure: ten head movements in vertical and then ten in horizontal direction covering an angle of 180 degrees in 0.8 s. The start of each series of standardized head movements was indicated by an auditory cue.

Test battery

The test battery consisted of different tasks used in previous MRI experiments (i.e. MRI-compatible) assessing: postural stability, oculomotor functions, vestibular related functions, and cognitive performance, see Figure 1B.

To assess postural stability a Romberg task was performed at two different levels, with feet in parallel and tandem position when standing barefoot with arms alongside the body and eyes closed. Stability was recorded by using a small accelerometer (83×51×9 mm, 47 gram) (DynaPort MiniMod, McRoberts Inc., the Netherlands). The meter was integrated in an elastic belt which was worn around the waist with the device located at the back close to the center of body mass. The devise contained three orthogonal linear accelerometers. The output signals were sampled with a sample frequency of 100 Hz, 16 Bits and a resolution of 0.30° (5.5 mG (1 mG≈ cm/s^2)). Data was stored on a removable SD card and acquired by special software (MiRA® version 1.9.1, McRoberts Inc., the Netherlands).

To test oculomotor functions, smooth pursuit and saccadic eye movements were assessed by asking the subject to actively track a stimulus over 10 degrees to each side in the horizontal plane. The stimulus was presented as yellow circle with diameter of 1˚ on a black screen. The sinusoidal pursuit stimulus moved at 0.2 Hz with peak velocity of 12.6˚/s. The saccadic stimulus was presented to the right, middle and left and vice versa at random interval times. Spontaneous eye movements (nystagmus) were assessed in darkness by asking the subject to look at an

imaginary point with eyes closed. Eye movements were recorded by horizontal electro-oculography over both eyes using three disposable electrodes (Blue sensor-N, AMBU, Denmark) of which one was attached at the outer side of the left and right eye and a reference electrode at the forehead. All data were registered and analyzed by BalanceLab software (Balance Lab, Jaeger-Toennies, Wurzburg and Maastricht Instruments v2.3.0.).

Several cognitive tasks were selected covering a broad range of domains. From more general functions like attention and concentration, towards vestibular related domains like spatial orientation. Similar to the MRI studies, effects on performance were expected to be subtle, acute and short-lived in educated and healthy individuals. Therefore, we assessed tasks that were relatively short (< 4 minutes for each sub-test) and insensitive to influences of practice and level of intelligence. For this reason we also included the time needed to complete a task as outcome measure in addition to task performance per se.

To measure the performance of memory (episodic learning) we used the Rivermead Behavioral Memory Test (RBMT) story recall for verbal memory (Wilson, Cockburn and Baddeley, 1989 in (Lezak et al. 2004)) and for nonverbal memory the Medical College of Georgia (MCG) figure (Loring and Meador, 2003 in (Lezak et al. 2004)). For working memory the short version of the WAIS III letter-number sequencing test (Wechsler, 1997 in (Lezak et al. 2004)) was administered twice throughout the test session by two different versions to check for a possible decrease in attention or motivation. To assess attention and concentration we selected two tasks; the symbol cancellation task (Diller, Ben Yishay et al., 1974 in (Lezak et al. 2004)) and a reaction time task with a simple-, complex- and inhibition level (van Zomeren et al. 1987; van Zomeren et al. 1984). Beside reaction time, this task also measures visuomotor performance, motion time and disengagement time by registration of initiation-, release-, movement- and return times of the home- and target button. The tests for visuospatial orientation were assessed on different aspects by the roadmap task for left-right orientation (Money, 1976 in (Lezak et al. 2004)), the judgment of line orientation task for angular relation (Benton et al. 1994), and the line bisection task for spatial representation (Schenkenberg et al., 1980 in (Lezak et al. 2004)). To explore the tactile modality, haptic perception was tested by use of the Kappers task (Kappers et al. 1999). Tests selected for visual perception included the visual tracking task (World Health 1986) and a visual acuity task (F.A.C.T.®). For integration of visual perception and motor performance the pursuit aiming task

(World Health 1986) was included. For a more detailed description of all these tasks see Figure 1B.

Data analysis

To statistically analyze the effect of exposure to GVS on test performance, linear mixed effects models in IBM SPSS Statistics 20.0 were used. Test performances were adjusted for practice effects, sex and sensitivity for motion sickness based on a priori answers to the motion sickness questionnaire. Subjects were included as random effects using heterogeneous compound symmetry. This assumes similar correlation between residuals of the same subject but no correlation between different subjects.

For every test the marginal means were estimated for each of the exposure conditions as follows:

$$\text{Marginal mean} = \text{Intercept} + R.C._{\text{exposure condition}} + 0.50*(\sum R.C._{\text{Session1+2}}) + (0.27*R.C._{\text{male}}+0.73*R.C._{\text{female}}) + (0.33*R.C._{\text{not motion sick}} + 0.63*R.C._{\text{moderate motion sick}} + 0.03*R.C._{\text{high motion sick}})$$

In which R.C. is the regression coefficient of the model for the specific factor and weighting factors were used for session (session 1 or 2), sex (N=8/30, [0.27] for being male and N=22/30, [0.73] for female) and motion sickness (low N=10/30, [0.33]; medium N=19/30, [0.63]; or high sensitivity N=1/30, [0.03]).

The data from the visual tracking task, roadmap, judgment of line orientation were first log(10) transformed to account for potential ceiling effects. Data of the postural stability tasks and saccadic latency were log(10) transformed to obtain a normal distribution. F.A.C.T. data were also log(10) transformed since the relationship between the steps is not linear (Gilmore 2002). The data of the RBMT story recall was converted into percentages of maximal possible score to obtain a normal distribution. Statistical significance level was defined as $p< 0.05$.

8.3 RESULTS

Descriptive results

All thirty subjects completed both experimental sessions resulting in 60 single data points per outcome measure. The number of the measurements included in the analysis varies per outcome, as a result of missing values. Due to a computer breakdown between 4 and 14 data points are missing, i.e. data of 2 complete subjects for the reaction task, 3 complete subjects and one measurement of 2 subjects for the postural stability tasks and 5 complete subjects and one measurement of 4 subjects for the oculomotor tasks. Unadjusted mean test scores and standard deviations in the two experimental conditions are presented in table 1 for postural stability and oculomotor tasks, and in table 2 for all neurocognitive tasks.

Effects of GVS

Table 3 shows the estimated mean performance on postural stability and oculomotor functions in the sham and GVS exposure condition based on the mixed model analyses, adjusted for potential confounding variables of session order, sex, and motion sickness. Exposure to GVS did not result in statistically significant nor consistent changes in performance on any of the tasks.

The adjusted mean performances of cognitive functions based on the mixed models are presented in table 4. Statistically significant negative effects of GVS on attention and concentration were present for speed of the pursuit aiming with small circles (-3.5%; p=0.004). Subjects dotted fewer items within circles in 60 seconds in the GVS condition compared to the sham condition. Visuomotor performance as defined by the pursuit precision (correct dots) was not affected by exposure to GVS, and neither were the parameters on the easier level of the pursuit aiming task with larger circles. On the contrary, visuomotor performance was borderline statistically significantly improved after GVS (4,6%; p=0.050) as reflected in the reduced motion time on the simple reaction task. This reduced time to release the home button and reach the target button indicates an improved coordination and faster response after GVS. Visuomotor performance on the more difficult versions of the reaction tasks, e.g. the complex and inhibition task, were not affected by GVS. Visual acuity as tested with the F.A.C.T. at 3.0 cpd. was significantly worse when exposed to GVS (-9.6%; p=0.035). However, none of the more difficult grating patches were affected

when exposed to GVS. None of the other cognitive tasks showed an effect of GVS when compared to the sham condition.

Effects of GVS versus MRI-related magnetic fields

Comparison of test performance on task level (direction and significance level) after GVS versus those previously found when exposed to MRI-related SMF in combination with movement-induced TVMF (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012), showed hardly any agreement, see Table 5. For example, pursuit aiming speed was not affected and motion time on the inhibition reaction task was borderline *improved* (p=0.05) when exposed to MRI-related magnetic fields (van Nierop et al. 2012). While visual acuity as assessed by the F.A.C.T. was also found to be poorer when exposed to MRI-related magnetic fields, this was seen at a different frequency level, i.e. 6.0 cpd. (p=0.025) (van Nierop et al. 2014).

When comparing results at the level of functional domains, only for attention and concentration weak similarities were found, i.e slower pursuit aiming speed after GVS exposure and slower disengagement time on the different levels of the reaction task after MRI-related field exposure (van Nierop et al. 2012). Other functional domains that were affected when exposed to MRI-related magnetic fields but not when exposed to GVS included a changed postural stability (van Nierop et al. 2013; van Nierop et al. submitted), spatial orientation (line-bisection) (van Nierop et al. 2012), verbal memory (RBMT) (van Nierop et al. 2014) and increased oculomotor function (saccadic velocity) (van Nierop et al. submitted).

Table 1 Average test performance and standard deviations (SD) for postural stability and oculomotor functions in the sham and GVS exposure condition calculated on untransformed data.

Domain	Test	Measure	#Obs.	Sham		GVS	
				Mean	SD	Mean	SD
Postural stability	Parallel 60 sec	Path	56	12.5	11.4	14.5	13.3
		Area	56	126.4	113.3	143.6	129.5
		Velocity	56	18.2	15.2	20.1	17.3
	Parallel 90 sec	Path	54	13.7	9.6	12.1	9.7
		Area	54	141.9	115.2	129.3	104.5
		Velocity	54	14.2	12.1	13.2	11.8
	Tandem	Path	52	34.4	27.4	29.9	21.3
		Area	52	289.8	227.2	256.6	169.9
		Velocity	52	87.4	65.6	81.5	59.3
Oculomotor function	Smooth pursuit	Gain	48	87.4	7.5	88.0	8.0
		Phase	48	-2.5	3.3	-3.5	3.0
	Saccades	Velocity-R	48	622.5	79.8	627.3	64.1
		Velocity-L	48	630.0	63.8	632.1	62.9
		Accuracy-R	48	92.6	7.1	93.8	8.4
		Accuracy-L	48	94.1	7.2	95.2	6.4
		Latency	46	109.9	6.0	108.5	5.0

Sway path in mm/s, sway velocity in mm/s^2, sway area in mm^2/s, Gain in percent, Phase in degree, Velocity in degrees per second, Accuracy in percent, Latency in milliseconds, #Obs is number of observations used in analysis

Table 2 Average test performance and standard deviations (SD) for each behavioral test in the sham and GVS exposure condition (60 observations, N=30) performed on untransformed data.

Test		Measure	Unit	Sham		GVS	
				Mean	SD	Mean	SD
RBMT		Immediate recall	points	10.2	3.9	10.9	4.4
		Delayed recall	points	9.4	3.4	9.2	4.4
		Difference (Δ)	%	94.2	23.43	83.2	21.7
MCG		Immediate recall	points	35.8	0.4	35.6	0.8
		Delayed recall	points	17.5	5.7	17.2	6.0
		Difference (Δ)	%	-18.4	5.6	-18.4	6.2
Letter-number		Points series 1	points	50.0	21.3	51.5	20.3
		Points series 2	points	55.6	16.1	52.2	17.2
		Difference (Δ)	points	-5.6	15.2	-0.7	17.9
Symbol cancellation		Speed	points	71.8	9.4	72.4	10.3
RT[1]	Simple	Reaction time	msec	339	38	333	26
		Motion time	msec	216	57	207	47
		Disengagement time	msec	122	29	122	28
	Complex	Reaction time	msec	391	43	386	32
		Motion time	msec	230	47	234	45
		Disengagement time	msec	126	28	122	25
	Inhibition	Reaction time	msec	426	49	432	44
		Motion time	msec	238	46	241	52
		Disengagement time	msec	125	28	126	30
Roadmap		Time	sec	42.3	15.8	42.3	15.1
JULO		Errors	points	2.7	2.1	2.8	2.0
Line bisection		Deviation	degrees	101.0	3.3	101.3	3.8
Kappers task		Deviation	degrees	24.29	13.5	24.02	14.9
Visual tracking		Time	sec	38.7	7.3	41.5	10.8
F.A.C.T.		1.5 cpd.	points	281.8	48.4	283.0	61.1
		3.0 cpd.	points	421.9	104.6	378.4	86.6
		6.0 cpd.	points	342.5	117.3	319.4	106.2
		12.0 cpd.	points	121.1	73.3	116.2	65.7
		18.0 cpd.	points	35.0	28.1	33.0	24.7
Pursuit aiming[1]	(S)	Speed	points	155.8	24.3	150.5	25.1
		Precision	%	91.3	6.1	90.0	6.6
	(L)	Speed	points	159.0	19.5	159.8	16.1
		Precision	%	93.9	4.6	92.9	3.9

Used units are explained in Figure 1B

[1]Reaction task had 56 observations (N=28) due to computer error. Pursuit aiming task small had 58 observations due to incorrect task assessment.

Table 3 Estimated marginal means for postural stability and oculomotor functions in the sham and GVS condition using a mixed effects model adjusted for session, sex and ever experienced mild motion sickness symptoms.

				95% CI		
			Estimate	Lower	Upper	p-value
Parallel 30 sec	Path[1]	Sham	9.7	7.5	12.5	
		GVS	10.8	8.4	14.0	0.441
	Area[1]	Sham	98.6	76.7	126.6	
		GVS	109.4	85.0	140.7	0.487
	Velocity[1]	Sham	12.1	8.6	17.1	
		GVS	12.9	9.1	18.3	0.645
Parallel 90 sec	Path[1]	Sham	10.9	8.3	14.3	
		GVS	9.2	6.9	12.2	0.193
	Area[1]	Sham	110.4	84.3	144.6	
		GVS	98.4	74.5	129.8	0.340
	Velocity[1]	Sham	9.4	6.7	13.2	
		GVS	8.5	6.0	12.0	0.368
Tandem	Path[1]	Sham	24.3	17.6	33.4	
		GVS	23.3	16.9	32.3	0.796
	Area[1]	Sham	203.2	147.8	279.9	
		GVS	200.0	144.5	277.2	0.914
	Velocity[1]	Sham	48.4	28.6	81.7	
		GVS	52.5	30.9	89.0	0.664
Smooth Pursuit	Gain	Sham	87.4	84.1	90.6	
		GVS	88.0	84.7	91.3	0.715
	Phase	Sham	-2.5	-3.9	-1.1	
		GVS	-3.7	-5.0	-2.3	0.061
Saccade	Velocity-R	Sham	623.7	594.2	653.3	
		GVS	626.8	597.0	656.6	0.852
	Velocity-L	Sham	631.7	606.4	657.0	
		GVS	634.9	609.5	660.3	0.810
	Accuracy-R	Sham	92.9	89.5	96.2	
		GVS	93.6	90.2	96.9	0.722
	Accuracy-L	Sham	93.8	91.1	96.6	
		GVS	95.2	92.4	98.0	0.394
	Latency[1]	Sham	115.3	106.9	124.5	
		GVS	110.9	102.8	119.7	0.437

[1]Back transformed results from log(10) analysis, therefore, no standard error can be calculated
Sway path in mm/s, sway velocity in mm/s^2, sway area in mm^2/s, Gain in percent, Phase in degree, Velocity in degrees per second, Accuracy in percent, Latency in milliseconds. For group sizes of analysis, see Table 1

Table 4 Estimated marginal means on cognitive functioning in the sham and GVS condition using a mixed effects model adjusted for session, sex and ever experienced mild motion sickness symptoms.

					95% CI		
	Measure	**Unit**		**Estimate**	**Lower**	**Upper**	**p-value[2]**
RBMT	Immediate recall	points	sham	10.2	8.8	11.6	
			GVS	10.9	9.6	12.3	0.225
	Delayed recall	points	sham	9.3	8.1	10.5	
			GVS	9.2	8.0	10.4	0.811
	Difference (Δ)	%	sham	94.5	86.6	102.4	
			GVS	83.2	75.3	90.1	0.086
MCG	Immediate recall	points	sham	35.7	35.5	36.0	
			GVS	35.7	35.5	35.9	0.801
	Delayed recall	points	sham	17.5	15.8	19.1	
			GVS	17.3	15.6	19.0	0.881
	Difference (Δ)	%	sham	-18.3	-20.0	-16.6	
			GVS	-18.4	-20.1	-16.7	0.908
Letter-number	Points series 1	points	sham	51.0	43.5	58.4	
			GVS	51.4	44.0	58.9	0.880
	Points series 2	points	sham	55.7	49.5	62.0	
			GVS	52.2	46.0	58.4	0.167
	Difference (Δ)	points	sham	-5.2	-10.9	0.5	
			GVS	-0.2	-6.0	5.4	0.201
Symbol cancel	Speed	points	sham	71.6	67.8	75.4	
			GVS	72.3	68.5	76.1	0.610
Simple RT	Reaction time	msec	sham	337.8	326.3	349.4	
			GVS	331.3	319.7	342.8	0.154
	Motion time	msec	sham	215.3	195.1	235.5	
			GVS	205.3	185.1	225.5	**0.050**
	Disengagement time	msec	sham	120.8	110.2	131.5	
			GVS	121.3	110.7	131.9	0.917
Complex RT	Reaction time	msec	sham	389.3	376.3	402.2	
			GVS	383.4	370.4	396.4	0.217
	Motion time	msec	sham	230.3	212.5	248.1	
			GVS	231.3	213.5	249.1	0.889
	Disengagement time	msec	sham	124.5	114.8	134.1	
			GVS	122.5	112.9	132.1	0.594
Inhibition RT	Reaction time	msec	sham	423.8	408.5	439.1	
			GVS	429.4	414.1	444.8	0.245
	Motion time	msec	sham	238.7	219.4	258.0	
			GVS	240.0	220.6	259.3	0.820
	Disengagement time	msec	sham	124.8	113.8	135.8	
			GVS	126.1	115.1	137.1	0.750
Roadmap	Time[1]	sec	Sham	39.8	35.3	44.9	
			GVS	39.9	35.4	45.0	0.913
JULO	Errors	points	Sham	2.6	1.9	3.4	
			GVS	2.9	2.1	3.6	0.555

Table 4 continued

					95% CI		
	Measure	**Unit**		**Estimate**	**Lower**	**Upper**	**p-value[2]**
Line Bisection	Deviation[1]	degrees	Sham	98.8	96.9	101.6	
			GVS	99.2	96.9	101.6	0.254
Kappers	Deviation	degrees	sham	23.7	18.8	28.5	
			GVS	23.0	18.2	27.8	0.684
Visual tracking	Time[1]	sec	sham	37.9	35.1	41.1	
			GVS	40.2	37.2	43.6	0.146
F.A.C.T.	1.5 cpd. [1]	points	sham	276.7	253.5	302.7	
			GVS	275.4	252.3	301.3	0.927
	3.0 cpd. [1]	points	sham	408.3	369.8	450.8	
			GVS	369.0	334.2	407.4	**0.035**
	6.0 cpd. [1]	points	sham	320.6	276.1	372.4	
			GVS	299.2	257.6	347.5	0.212
	12.0 cpd. [1]	points	sham	101.9	76.2	136.1	
			GVS	91.2	68.1	121.9	0.378
	18.0 cpd. [1]	points	sham	26.6	19.6	34.4	
			GVS	26.0	20.0	35.2	0.811
Pursuit aiming Small circles	Speed	points	sham	154.2	145.5	162.9	
			GVS	148.8	140.1	157.5	**0.004**
	Precision	%	sham	91.2	88.9	93.5	
			GVS	89.8	87.5	92.1	0.138
Large circles	Speed	points	sham	159.3	152.7	165.8	
			GVS	160.1	153.6	166.6	0.768
	Precision	%	sham	93.8	92.3	95.3	
			GVS	92.8	91.3	94.3	0.131

[1] Back transformed results from a Log10 analysis, therefore, no standard error can be calculated

[2] Bold values statistical significant at $p \leq 0.05$

For group sizes of analysis, see Table 2

Table 5 Direction and significance of acute changes on task performance when exposed to MRI-related magnetic fields and GVS for tasks on which a statistical significant effect of exposure was found in at least one of the three experiments

Domain	Task		MRI (exp 1) [1]		MRI (exp 2) [2]		GVS	
			Direction	p-value	Direction	p-value	Direction	p-value
Memory	RBMT	Delayed recall	Worse	0.12	Worse	**0.04**	Worse	0.82
Attention	Simple RT	Diseng. time	Worse	**<0.01**	Worse	0.09	Worse	0.92
	Complex RT	Diseng. time	Worse	**<0.01**	Worse	0.10	Better	0.59
	Inhibition RT	Diseng. time	Worse	**0.01**	Worse	0.53	Worse	0.75
	P. Aiming (S)	Speed	Better	0.36	Worse	0.69	Worse	**<0.01**
Spatial orientation	Line Bisection	Deviation	Worse	**0.05**	Worse	0.39	Better	0.25
Visual perception	F.A.C.T.	3.0 cpd.	Better	0.27	Better	0.06	Worse	**0.04**
		6.0 cpd.	Worse	0.42	Worse	**0.03**	Worse	0.21
Visuomotor performance	Simple RT	Motion time	Worse	0.56	Worse	0.51	Better	**0.05**
	Complex RT	Motion time	Worse	0.56	Worse	0.30	Worse	0.89
	Inhibition RT	Motion time	Worse	**0.05**	Better	0.93	Worse	0.82
Postural stability	Parallel 30 sec	Path	Worse	**0.02**	Better	0.07	Worse	0.44
	Parallel 90 sec	Path	-	-	Better	**0.01**	Better	0.19
Oculomotor functions	Saccade	Velocity-R	-	-	Better	**<0.01**	Better	0.85
		Velocity-L	-	-	Better	**<0.01**	Better	0.81

[1]MRI experiment 1 (van Nierop et al. 2013; van Nierop et al. 2012); p-value reflects SMF+TVMF condition compared to sham+HM condition; p-value postural stability reflects performance using TVMF exposure proxy versus sham+HM. [2]MRI experiment 2 (van Nierop et al. submitted; van Nierop et al. 2014); p-value reflects SMF+TVMF condition compared to sham+HM condition. Abbreviations; reaction task (RT) task not assessed (–), pursuit aiming task small circles (S). Models of all three experiments are adjusted for session, sex and motion sickness

8.4 DISCUSSION

The aim of the current study was to compare test performance after GVS with test performance as found during exposure to SMF of an MRI scanner (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012). Based on previous studies we expected GVS at 1.0 mA to be able to influence selected outcome measures. For example, postural stability (Rinalduzzi et al. 2011; Wardman et al. 2003a; Wardman et al. 2003b) and oculomotor functions could be affected as a result of induced spontaneous horizontal (Aw et al. 2006; Severac Cauquil et al. 2003) and torsional eye movements (Severac Cauquil et al. 2003; Winther et al. ; Zink et al. 1998). In addition, we postulated that performance on tasks using spatial orientation paradigms (Ferre et al. 2013b) like the line bisection task, judgment of line orientation and Kappers task could have been influenced since the subjective vertical is known to be affected by GVS (Mars et al. 2001; Tardy-Gervet et al. 1998). Mental transformation (Lenggenhager et al. 2008) as tested by the Roadmap could have been affected depending on the use of allo- or ego centric orientation (Dilda et al. 2012; Fink et al. 2003; Lenggenhager et al. 2008).

The results of this study demonstrate that low intensity bipolar binaural galvanic vestibular stimulation at 1.0 mA and 0.4 Hz did deteriorate attention and concentration (pursuit aiming speed; $p=0.004$), decreased visual acuity (F.A.C.T. at 3.0 cpd. $p=0.035$) and improved visuomotor performance (motion time on a reaction task; $p=0.05$). Although these results demonstrate that GVS affects cognitive performance, some limitations need to be taken into account regarding these findings. Since a deteriorated attention and concentration was demonstrated on the pursuit aiming task we also expected to see this trend in other tasks requiring high concentration levels like in the reaction task. However, no effect on attention was revealed for the reaction time and disengagement time at all levels of the reaction task. The improved visuomotor performance after GVS for motion time at the simplest level of the reaction task was surprisingly not confirmed in the more difficult levels of complex and inhibition reaction task. Other cognitive tasks, postural stability, vestibular-ocular reflex and oculomotor functions were not affected.

Comparison of test performance on task level and domain level (direction and significance level) after GVS versus those previously found when exposed to MRI-related SMF in combination with movement-induced TVMF (van Nierop et al.

2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012), showed hardly any agreement. When a similar response pattern would have been demonstrated this would have supported the hypothesis that the vestibular system plays a role in MRI-related magnetic field induced behavioral changes. However, a dissimilar response pattern cannot exclude a mediating role of the vestibular system in MRI-related magnetic field induced behavioral changes. Therefore, based on our findings we cannot confirm the hypothesis that the vestibular system plays a (mediating) role in MRI-related magnetic field induced behavioral changes, neither can we rule out this possibility. GVS might not be an appropriate model for MRI-related magnetic field stimulation of the vestibular system.

The behavioral changes of GVS as found in this study can be interpreted in different ways.

Firstly, the vestibular system is possibly not alone involved in evoking behavioral changes upon MRI-related static magnetic field exposure. This is in line with experimental MRI research in the homogeneous static magnetic fields of the bore, where exposure to >3.0 Tesla SMF is proven to stimulate the rotary sensors in the semicircular canals of the labyrinth by inducing vestibulo-ocular reflex (VOR) related nystagmus (Antunes et al. 2012; Roberts et al. 2011; Ward et al. 2014) but did not induce cognitive changes (Heinrich et al. 2013; Lepsien et al. 2012) . This suggests that the changes of postural instability and decreased cognitive functions in the stray SMF of the MRI in combination with movement-induced TVMF might be mediated by another working mechanism than the vestibular system per se, e.g. sensory conflict theory, sensory weighting theory or information processing capacity theory (Van Nierop 2015). For these theories exposure to a combination of SMF and TVMF seems necessary in evoking behavioral changes.

Secondly, the used GVS did not reflect vestibular stimulation as induced by MRI-related magnetic fields. The applied stimulation intensity of 1.0 mA was possibly not strong enough to induce either a postural, VOR or oculomotor changes (Dilda et al. 2012; Moore et al. 1991). Habituation to the repeated GVS stimulus might also have played a role (Balter et al. 2004). Although at 1.0 mA DC stimulation VOR mediated- and postural changes were demonstrated by others (Aw et al. 2006; Rinalduzzi et al. 2011; Severac Cauquil et al. 2003; Wardman et al. 2003a; Wardman et al. 2003b). In our study GVS with AC was used to simulate the sinusoidal pattern which is evoked by head movement-induced TVMF within the

MRI studies. It is unknown what the results would have been with AC instead of DC.

Lastly, a disadvantage of the inseparable combination of head movements and TVMF as present within MRI settings is that in the GVS experiment a condition with galvanic stimulation during head movements had to be applied. In practice this restricted the setup by measuring test performance only after exposure to GVS and performance of head movements, instead of during GVS exposure (which was done in previous GVS experiments). Therefore, a plausible explanation for the absence of more pronounced findings is that the behavioral changes faded away too quickly after GVS exposure has stopped. It has been demonstrated that postural stability returned to baseline when GVS is removed (MacDougall et al. 2006). This also applies for induced torsional eye movements, when the stimulus is switched off the eyes rotated in the opposite direction back to their normal position (Severac Cauquil et al. 2003). When behavioral changes fade away quickly after stimulation of the vestibular organ has ended, it seems reasonable that test performance is stronger influenced by SMF as by TVMF within the stray fields of the MRI scanner since after performance of head movement (i.e. exposure to TVMF), SMF exposure is still present during task assessment.

This study was designed to compare effects of GVS exposure on test performance with the results as found in earlier experiments with exposure to MRI-related SMF and TVMF (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012). Therefore the experimental setup e.g. stimulation during performance of head movements prior to a task and stimulation characteristics were similar to previous experiments with TVMF exposure. Simulation of the SMF exposure condition as present in the MRI experiment was not preferred since continuous exposure to GVS for longer periods results in painful sensations at the skin under the electrodes and feeling of discomfort. A different design could be used with stimulation during task performance only (preceded with or without performance of head movements) alternated with periods of no stimulation; this however does not mirror MRI exposure patterns.

An improvement in the study design is therefore hard to achieve but stimulation intensity can be mimicked. To guarantee stimulation at sub-sensory levels individual threshold levels can be identified beforehand. This can even result in stimulation levels above 1.0 mA for certain individuals. Also higher stimulation

intensities can result in the expected sensory effects of dizziness etc., which are consequently more likely to directly impair test performance. To improve the exposure setup blinding of the experimenter and subject could be achieved by programming the computer which controls the electrodes, but when sensory effects occur blinding will be impossible. Moreover, behavioral responses to GVS vary considerably between healthy subjects (Coats 1973b; MacDougall et al. 2002; Mars et al. 2005), this resulted in a large variability in performance after GVS compared to performance during MRI exposure. This indicates we would need much larger subject groups to detect significant changes than when testing in an MRI environment.

The participating subjects were not informed about the specific exposure conditions or about applied order of treatment. Based on a questionnaire at the end of each session, the subjects guessed 'no exposure' or 'exposure' correctly in 70% of the sham conditions and 63% of the exposure conditions suggesting that blinding was not entirely successful. Answers to the post-session questionnaire showed that the subjects chose for 'no exposure' when no physical symptoms were perceived. Moreover, according the subjects, exposure to GVS was evident when symptoms like tingle at the mastoid and dizziness occurred.

In conclusion, certain outcome measures of attention and concentration, visuomotor performance and visual acuity were statistically significantly affected by low intensity bipolar binaural GVS at 1.0 mA and 0.4 Hz, yet effects of GVS were not consistent within tasks and functional domains. Postural stability, VOR and oculomotor functions were not affected after GVS exposure. Comparison of test performance on task level and domain level (direction and significance level) after GVS versus those previously found when exposed to MRI-related SMF in combination with movement-induced TVMF (van Nierop et al. 2013; van Nierop et al. submitted; van Nierop et al. 2014; van Nierop et al. 2012), showed hardly any agreement. Based on these findings we cannot confirm the hypothesis that the vestibular system plays a (mediating) role in MRI-related magnetic field induced behavioral changes, neither can we rule out this possibility.

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SUPPLEMENTAL MATERIAL

Table S1 Mean test scores and standard deviations (SD) in the sham condition (with additional head movements before the tasks), in previous experiment MRI 1 (van Nierop et al. 2012) (N=30), MRI 2 (van Nierop et al. submitted) (N=36) and current GVS experiment (N=30).

			Sham MRI 1		Sham MRI 2		Sham GVS	
Domain	**Test**	**Measure**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Postural stability	Parallel 30 sec	Path	10.7		12.8	9.9	12.5	11.4
		Area	125.0		132.0	112.4	126.4	113.3
		Velocity	16.3		17.1	12.6	18.2	15.2
	Parallel 90 sec	Path	n.a.		11.1	9.4	13.7	9.6
		Area	n.a.		128.6	98.7	141.9	115.2
		Velocity	n.a.		13.9	12.0	14.2	12.1
	Tandem	Path	50.5		46.0	37.4	**34.4**	27.4
		Area	368		375.8	329.9	**289.8**	227.2
		Velocity	84.4		116.7	89.2	**87.4**	65.6
Oculomotor function	Smooth	Gain	n.a.		88.2	5.8	87.4	7.5
		Phase	n.a.		-2.5	1.8	-2.5	3.3
	Saccades*	Velocity-R	n.a.		400.3	41.9	**622.5**	79.8
		Velocity-L	n.a.		408.1	47.6	**630.0**	63.8
		Accuracy-R	n.a.		95.4	5.4	92.6	7.1
		Accuracy-L	n.a.		94.9	4.8	94.1	7.2
		Latency	n.a.		110.6	8.0	109.9	6.0

All data represent raw, untransformed data; n.a. not assessed
Bold values; more than 20% difference of between sham condition between current and MRI experiment(s).

Table S2 Mean test scores and standard deviations (SD) in the sham condition of MRI experiment 1 (van Nierop et al. 2012) (N=30), MRI 2 (van Nierop et al. submitted) (N=36) and current experiment (N=30).

			Sham MRI 1		Sham MRI 2		Sham GVS	
Test	**Measure**	**Unit**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
RBMT	Immediate recall	Points	10.1	3.4	12.1	3.6	10.2	3.9
	Delayed recall	Points	9.5	3.3	10.7	3.4	9.4	3.4
	Difference (Δ)	%	93.9	16.6	89.0	14.6	94.2	23.43
MCG	Immediate recall	Points	35.7	0.7	n.a.	n.a.	35.8	0.4
	Delayed recall	Points	20.8	4.8	n.a.	n.a.	17.5	5.7
	Difference (Δ)	%	-14.9	4.6	n.a.	n.a.	-18.4	5.6
Letter-number	Points series 1	Points	45.6	16.4	n.a.	n.a.	50.0	21.3
	Points series 2	Points	46.8	20.8	n.a.	n.a.	55.6	16.1
	Difference (Δ)	Points	**-1.4**	**20.2**	n.a.	n.a.	**-5.6**	**15.2**
Symbol cancel.	Speed	Points	73.4	10.7	n.a.	n.a.	71.8	9.4
RT Simple[h]	Reaction time	msec	331	41	333.2	37.3	339	38
	Motion time	msec	217	54	223.2	58.1	216	57
	Disengagement time	msec	116	36	129.7	34.4	122	29
RT Complex[h]	Reaction time	msec	395	45	390.0	45.8	391	43
	Motion time	msec	240	58	246.6	58.8	230	47
	Disengagement time	msec	124	20	128.2	31.8	126	28
RT Inhibition[h]	Reaction time	msec	443	55	424.9	44.4	426	49
	Motion time	msec	241	56	257.4	67.9	238	46
	Disengagement time	msec	125	27	131.1	27.8	125	28
Roadmap	Time	sec	50.2	20.7	n.a.	n.a.	42.3	15.8
JULO	Errors	Points	2.4	2.1	n.a.	n.a.	2.7	2.1
Line bisection	Deviation	Degrees	**100.3**	**6.7**	**101.6**	**7.0**	**101.0**	**3.3**
Kappers task	Deviation	Degrees	**56.5**	**29.4**	n.a.	n.a.	**24.29**	**13.5**
Visual tracking	Time	Sec	39.1	12.6	n.a.	n.a.	38.7	7.3
F.A.C.T.	1.5 cpd.	Points	303.3	42.8	299.7	41.2	281.8	48.4
	3.0 cpd.	Points	400.5	98.6	413.3	103.4	421.9	104.6
	6.0 cpd.	points	316.5	125.9	344.4	121.9	342.5	117.3
	12.0 cpd.	Points	101.8	68.6	113.6	73.1	121.1	73.3
	18.0 cpd.	Points	29.4	14.8	31.1	27.2	35.0	28.1
Pursuit aiming (S)	Speed	Points	148.0	13.9	140.8	15.2	155.8	24.3
	Precision	%	81.5	7.3	78.3	9.6	91.3	6.1
(L)	Speed	Points	156.3	15.9	147.7	15.2	159.0	19.5
	Precision	%	94.1	3.2	92.1	5.0	93.9	4.6

All data represent raw, untransformed data; n.a. not assessed.

Reaction task had only 28 observations (N=28) due to computer error. Pursuit aiming task small had only 29 observations due to incorrect task assessment. Bold values; more than 20% difference of between sham condition between current and MRI experiment(s). **RBMT** in correct recalled words; **MCG** in correct recalled lines; **Letter-number** in correct items of longest row multiplied by amount of correct recalled rows; **Symbol cancellation** speed is calculated as correct scored items in 60 seconds; **RT Simple** (1 button option); **Complex** (9 button options); **Inhibition** (button left from target button, 8 options), Reaction time is time release of home button after stimulus. Motion time is time needed to go from home button to target button. Disengagement time is time needed to release the target button all given in msec; **Roadmap** in time (in sec) to complete task; **JULO** amount of false judged lines; **Line Bisection** deviation (in percent) from true middle of the line (100%); **Kappers task** in average deviation from reference bar (in degrees); **Visual tracking** in time to complete the task (in sec); **F.A.C.T.** Contrast sensitivity level in cycles per degree; **Pursuit Aiming** Small (S) and Large (L) circles, speed is calculated as correct scored items in 60 seconds. Precision is calculated as total correct responses divided by total amount of responses in 60 seconds.

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Chapter 9

General Discussion

The growing popularity of MRI in clinical settings and the innovative applications in e.g. MRI guided surgery have resulted in longer and more frequent exposure to stray magnetic fields from MRI scanners for employees. With the use of stronger field strengths in MRI, unwanted sensory symptoms and changes in task performance have been observed and reported. This has raised the need to further explore biological and health effects from exposure to strong MRI-related static magnetic fields (SMF) and motion induced low-frequency time-varying magnetic fields (TVMF). In this thesis three objectives have been addressed in order to identify acute behavioral changes following exposure to MRI-related magnetic stray fields and to explore and hypothesize underlying mechanisms.

I. Domains and functions affected by stray magnetic fields

It is essential to first identify and map relevant behavioral functions that could be affected when exposed to MRI-related stray magnetic fields. In two experimental studies we assessed a broad range of cognitive functions relevant for medical professionals, e.g. surgeons and others operating near MRI systems. In addition, as it has been suggested that magnetic fields might interact with the vestibular system, we also have evaluated vestibular related functions. In these two studies healthy subjects were exposed to the stray SMF of a 7 Tesla (T) MRI system using a double blind randomized cross-over design. In selected exposure conditions additional low-frequency TVMF were induced, before every single task, by standardized head movements. Of all the tasks assessed we demonstrated a decreased eye-hand coordination, spatial orientation, attention and concentration (van Nierop et al. 2012), visual acuity, and verbal memory (van Nierop et al. 2014). However, not all affected functions showed a similar direction in results over both experiments. Results on spatial orientation and visual acuity in the first experiment (van Nierop et al. 2012) were not replicated in the second experiment (van Nierop et al. 2014), whereas results for attention and concentration, visuomotor performance and verbal memory were in the same direction between experiments (van Nierop et al. 2014; van Nierop et al. 2012).

Earlier studies already indicated a negative impact of exposure to movement in a stray static magnetic field (SMF+TVMF) on eye-hand coordination (de Vocht et al. 2006; de Vocht et al. 2003), visual tracking speed (de Vocht et al. 2007; de Vocht et al. 2006) , and visual and auditory working memory (de Vocht et al. 2006). Although current and previous studies do not show similar tasks affected, exposure

to SMF and low-frequency TVMF often appear to decrease performance per se. Generally, cognitive domains that have consistently shown to be affected include: verbal memory, visuo(motor) functions, and attention and concentration.

Vestibular related functions that were identified within the two experimental studies included a decreased postural stability (van Nierop et al. 2013) and change in oculomotor function of saccadic velocity (van Nierop et al. submitted-b) when exposed to the stray SMF in combination with low-frequency movement induced TVMF. However, the strongly reduced postural stability as found in the first experiment (van Nierop et al. 2013) was not demonstrated in the second experiment (van Nierop et al. submitted-b).

These observed behavioral changes when exposed to 1.0 T SMF and a low-frequency induced TVMF of 2.4 T/sec, can be relevant for professionals working in these fields on a daily basis.

II. Stray static magnetic fields versus in time-varying magnetic fields

Up till now, all observed behavioral changes within experimental studies were identified when exposed to the combination of stray SMF and head movement induced TVMF. Since the stray SMF is always present around an MRI system in stand-by modus, it is possible to disentangle effects from exposure to SMF only and from exposure to a combination of SMF and movement induced TVMF, but not the separate effect of movement induced TVMF. Dissociating effects of SMF and SMF+TVMF might point to different working mechanisms and might implicate different control measures if needed.

In the second experiment, test performance in the SMF only and SMF+TVMF conditions were compared to corresponding sham conditions (e.g. with and without head movements). In this experiment only a decreased verbal memory and changed oculomotor function were revealed when exposed to the magnetic fields (van Nierop et al. submitted-b; van Nierop et al. 2014). The decrease in verbal memory was attributed to the combination of SMF and TVMF rather than exposure to SMF alone (van Nierop et al. 2014), while for oculomotor function, exposure to SMF seemed to determine change in saccadic velocity rather than exposure to a combination of SMF+TVMF (van Nierop et al. submitted-b). Other earlier identified cognitive functions of visuomotor performance, spatial orientation, and attention and concentration were not affected in the SMF or in the SMF+TVMF condition.

III. Indications for a working mechanism; involvement of the vestibular system

For some of the reported sensory symptoms a working mechanism via the vestibular system has been suggested (Glover et al. 2007). Therefore, a mediating role for the vestibular system underlying the magnetic field induced behavioral changes was investigated by two different approaches. Firstly, we investigated whether responsiveness of the vestibular system modifies test performance upon magnetic field exposure. Secondly, we compared test performance after direct vestibular stimulation with test performance during MRI-related magnetic field exposure.

Responsiveness of the vestibular system

Test performance within the stray magnetic fields was studied in a second experiment (Van Nierop et al. submitted-a) among subjects with relatively normal versus high vestibular responsiveness. Based on several measures representing vestibular responsiveness, it became clear that highly responsive subjects did not show a different response than normally responsive subjects on cognitive tasks and oculomotor functions. However, a consistent change of improved postural stability in subjects with a relatively high vestibular unilateral weakness was revealed when performing head movements within the SMF. Possibly subjects with an asymmetry between vestibular labyrinths use the magnetic field as an orientation frame to control body movement. In contrast, subjects without unilateral weakness showed a decreased postural stability in the SMF+TVMF condition, as was also found among all volunteers in experiment 1. Taken together, magnetic field induced behavioral changes and oculomotor functions were not modified by vestibular responsiveness, whereas postural stability seemed to be modified by vestibular unilateral weakness. This indicates an improved balance upon exposure among subjects with unilateral weakness and a decreased balance in others. In this first attempt to study the role of vestibular responsiveness, findings should be interpreted with caution since they are based on relatively small groups.

Galvanic vestibular stimulation

When stimulating the vestibular system in a direct and controlled manner, the resulting pattern in behavioral responses can be compared to those in experiments with exposure to stray magnetic fields from an MRI system. A similar behavioral response pattern would indicate a mediating role for the vestibular system in MRI-

related magnetic field induced effects. However, a dissimilar response pattern cannot exclude a mediating role of the vestibular system in MRI-related magnetic field induced behavioral changes.

In a third experimental study, test performance on cognitive, postural and oculomotor tasks was studied after Galvanic Vestibular Stimulation (GVS) (Van Nierop submitted). In a balanced randomized cross-over design, healthy volunteers underwent GVS (binaural bipolar sinusoidal with peak amplitude of 1.0 mA and 0.4 Hz) and 'sham' stimulation (0 mA and 0 Hz) during performance of standardized head movements for 20 seconds prior to each task of the test battery. Head movements were performed to resemble the SMF+TVMF condition in the MRI experiment, for reasons of comparability.

Although significant effects of GVS were demonstrated for the domains of attention and concentration, visuomotor performance and visual acuity, these findings were not consistent within tasks or within functional domains between GVS and MRI exposure. Moreover, the behavioral response pattern on GVS did not resemble those after exposure to an MRI-related stray magnetic field. In conclusion, these results do not support the hypothesis that the vestibular system plays a (mediating) role in MRI-related magnetic field induced behavioral changes.

Experimental design

The two experimental MRI studies described in this thesis used a double blind balanced randomized sham-controlled cross-over design (Chalmers et al. 1981; Maclure et al. 2000). Double blind refers to blindly guiding the subjects and experimenters to the test location (Aldinucci et al.), so both subject and experimenter were unaware of the exposure condition, minimizing the psychological effects of knowing exposure is present. Randomized sham-controlled cross-over design means that subjects received all the different exposure and sham condition(s), in a randomized order, eliminating a practice effect. Every order of exposure and sham was equally divided over the subjects as indicated by a balanced distribution. The GVS study used a single blind design due to administration restrictions of the GVS apparatus. Consequently, in the GVS experiment only the subject was blinded for true or false GVS exposure. Experimenters might (unconsciously) act differently, e.g. stimulate performance, when knowing exposure is on or off.

The use of a double blind balanced randomized sham-controlled cross-over design provides the most reliable representation of the actual outcome measure(s), since interaction of confounding covariates are eliminated by subjects serving as their own controls. This design is also statistically efficient as fewer subjects are needed compared to other type of designs. Any possible induced 'carry over' effects or 'order of treatment effects' were limited by a break of at least 30 minutes after exposure and by randomization of the order of the experimental sessions. A remaining learning effect, which always occurs when administering the same or similar test multiple times in row, was adjusted for by including the session number as a covariate in the linear mixed models.

Exposure assessment methods

In order to have similar exposure conditions between subjects the test positions were fixed to a location defined by stationary measurements with a three-axis Hall Magnetometer at a presumed head height in sitting position of 150 cm. The location with the highest possible exposure to stray SMF was chosen to position subjects; this was a 1000 mT SMF, 47 cm in front of the bore at centerline. A second location was defined 86 cm in front of the bore with an exposure of 500 mT SMF in experiment 1.

To define exposure to SMF and TVMF during the course of the experiment, the subjects wore a helmet with a magnetic field dosimeter (University of Queensland, Australia (Fuentes et al. 2008)) attached inside. This dosimeter indicated that performance of standardized head movements induced a TVMF of 2400 mT/s and 1400 mT/s, for the 1000 mT and 500 mT exposure conditions respectively. The results of the statistical analyses using quantitative personal exposure measurements instead of distance defined categories resulted in similar associations between exposure and test performances on a reaction task and line bisection task (van Nierop et al. 2015). Therefore, we concluded that in a controlled experimental setup, exposure categories based on distance to the bore is a good proxy for personal exposure when placing subjects at fixed positions with standardized head movements in the magnetic stray fields of a 7 T MRI. As a result, in the second experiment, exposure categories were based on distance to the bore. Differences in effects of magnetic fields on behavioral measures between experiments 1 and 2 are likely not attributable to the small differences in exposure that might have occurred.

Statistical analysis

For estimating inter-individual differences in test performance in a case-crossover design, we used multivariate linear mixed effects models adjusted for potential confounding variables, such as session number, gender and reported susceptibility to motion sickness. The random effects were modeled using heterogeneous compound symmetry which assumes similar correlation between residuals of the same subject but no correlation between different subjects.Task performance of vestibular responsive groups was tested with the same model and confounding factors, but without reported susceptibility to motion sickness. In addition, the interaction between vestibular responsive groups with magnetic field exposure was studied.

A mixed model is a relative general model since it addresses both fixed and random factors, and it takes into account the correlation of repeated measurements within subjects. We preferred this model because we did not have to exclude subjects when they had missing observations. An additional advantage of this approach is that it also provides effect sizes (regression coefficients/betas and confidence intervals) in addition to p-values.

Because multiple behavioral outcome measures were assessed in these studies it could be defensible to adjust for multiple testing. However, multiple

testing is based on p-values and is not about effect sizes. Moreover, we study biological mechanisms and not random numbers, therefore the increased chance of a type 1 error (detecting an effect that is not present) is not applicable (Rothman 1990; Rothman 2014), making adjustments for multiple testing superfluous.

Difference in experimental characteristics

As a consequence of the specific objectives studied in each of the three experimental studies, different approaches and experimental setups were used, see table 1. This could have attributed to test results that were not always consistent at task level between experiments.

- Subject population; based on self-reported vulnerability to motion sickness on a MSSQ (Golding 1998), volunteers were excluded (experiment 1) or included to have a distribution of subjects from *not* to *very susceptible* to motion sickness (experiment 2), see appendix table 1. Assuming that susceptibility to motion sickness is a modulating factor, this could have resulted in larger between subject variability in test performance as shown by the larger standard deviations in test outcomes and consequently in fewer statistically significant results in the second experiment. However, in experiment 2 we found no indications that subjects with a higher score on the MSSQ indeed responded differently upon MRI exposure, as no significant interactions were found.
- Exposure duration; in the second experiment we assessed a more concise test battery than in the first experiment. This has resulted in different exposure durations for SMF (30 versus 65 minutes respectively) and TVMF (16 versus 21 times respectively). Longer exposure duration might have led to fatigue or emerging motion sickness, resulting in decreased concentration and task performance, potentially enhanced by effects of exposure.
- Number of exposure conditions: in experiment 1 we studied exposure-response relationships (1.0 T and 0.5 T versus 0 T). This may have resulted in more power to detect subtle effects of exposure in experiment 1 compared to experiment 2 (and 3) in which just one level of exposure was studied (1.0 T or GVS respectively versus sham).

Table 1 Overview of experimental characteristics

		Experiment 1	Experiment 2	Experiment 3
Exposure		MRI	MRI	GVS
Main aim		-Identify relevant affected tasks and domains -Study exposure-response relationship	-Separate effects of SMF from those of SMF+TVMF -Explore whether vestibular responsiveness modifies effects of SMF and SMF+TVMF	Explore whether direct vestibular stimulation results in a similar response pattern compared to SMF (+TVMF) exposure
Exposure Conditions[2]	**1.** **2.** **3.** **4.**	0 T + HM 0.5 T + 1.2 T/s by HM 1.0 T +2.4 T/s by HM	0 T 0 T +HM 1.0 T 1.0 T +2.4 T/s by HM	Sham + HM GVS 0.4mA + HM
Time between sessions		1 week	1 or 24 hours[1]	1 hour
Duration of test battery		65 min	30 min	65 min
Exposure duration[2]		65 min SMF 21 times 20 sec. TVMF by HM	30 min SMF 16 times 20 sec. TVMF by HM	25 times 20 sec GVS and HM
Test battery		18 cognitive tasks 2 balance tasks	9 cognitive tasks 3 balance tasks 3 oculomotor tasks	18 cognitive tasks 3 balance tasks 3 oculomotor tasks
Test after exp. sessions		-	Caloric reflex test Rotary chair test	-
Subject population		30 healthy volunteers, not vulnerable to motion sickness	36 healthy volunteers	30 healthy volunteers, not vulnerable to motion sickness
Test design		Double blind balanced randomized cross over	Double blind balanced randomized cross over	Single blind balanced randomized cross over

[1] 1 hour for corresponding sham/exposure and 24 hours for the other exposure/sham pair
[2] HM; head movements, performed before each test

Differences in findings at task level between our studies and earlier conducted studies in the stray magnetic fields by e.g. de Vocht et al. and Glover et al. can be explained by differences in experimental setups; e.g. testing in a single blind design, use of a population occupationally familiar with MRI, and exposure conditions which were not randomized, could have overestimated the actual behavioral changes (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; Glover et al. 2007). Moreover the use of lower exposure levels (below 1.0 T SMF), smaller angle of head or body rotations (90 degrees) inducing a lower TVMF exposure (maximum 0.3 T/s), shorter exposure duration, and fewer subjects (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; Glover et al. 2007) could have resulted in lower effect estimates. Despite these differences in experimental designs all studies identified corresponding functions affected by exposure to MRI-related magnetic fields, e.g. attention and concentration, verbal memory, visuo(motor) performance, and postural stability.

Working mechanisms

Over the years, different working mechanisms have been proposed predominantly for explaining the magnetic field induced sensory responses, such as metal taste and vertigo (Glover et al. 2007; Schenck 2005). With regard to our identified behavioral changes of decreased cognitive functions, postural stability and oculomotor function due to magnetic field exposure we put several of these mechanisms into a framework, see Figure 1 and will elaborate upon them below. Some (reciprocal) (inter)actions between fields, forces, affected areas, hypothetical mechanisms and behavioral outcomes are not depicted and not discussed for simplicity.

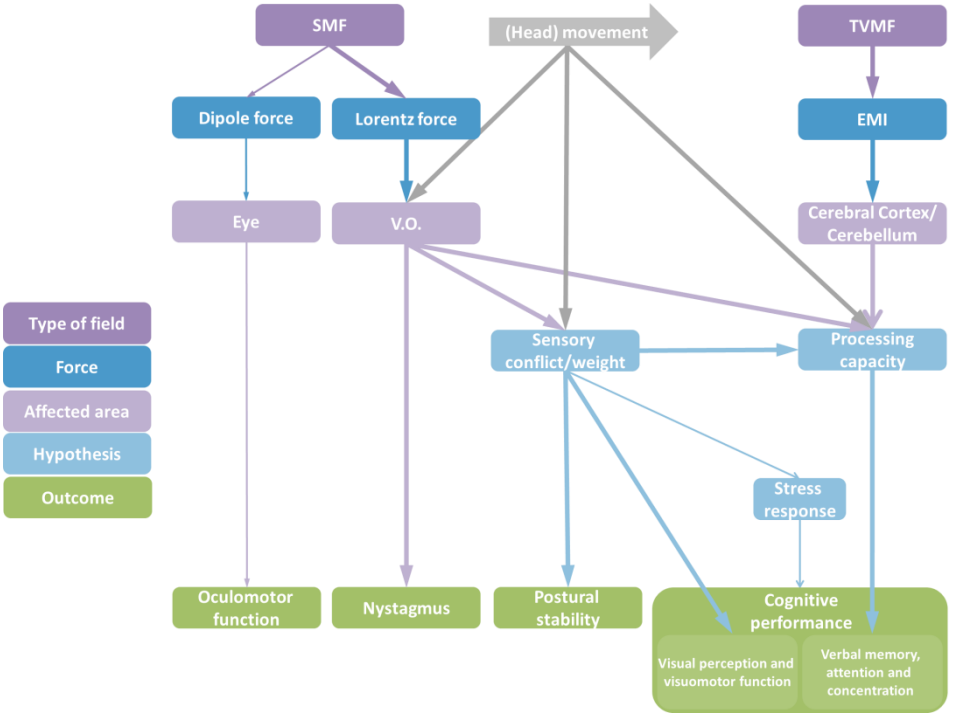

Figure 1 Proposed working mechanisms of exposure to static (SMF) and time-varying magnetic fields (TVMF) on behavioral measures of oculomotor function, nystagmus, postural stability and conceptual endpoints of cognitive performance.
Thick arrows indicate the most likely pathways of action. Thin arrows indicate possible action pathways. Abbreviations: SMF, static magnetic field; TVMF, time-varying magnetic field; EMI, electromagnetic induction; V.O., vestibular organ (as target organ of the vestibular system); VOR, vestibular-ocular reflex.

Lorentz force (and the vestibular organ)

The Lorentz force is a component of the Magnetohydrodynamics (MHD) equation. MHD describes the motion of a conducting fluid in a magnetic field where Lorentz forces depend on an intrinsic moving fluid instead of an active moving body. It has only recently been suggested that the interaction between a SMF and naturally occurring ionic currents in the endolymph fluid of the vestibular labyrinth, result in a Lorentz force (Roberts et al. 2011). This force pushes on the cupula of the semicircular canal (SCC), transducing a signal of head rotation to the vestibular afferent, see Figure 2.

This mechanism was verified in healthy and in vestibular deficit subjects lying in supine position on the scanner bed of a ≥ 3.0 T MRI in total darkness, i.e. with field lines in caudal direction. In healthy subjects stimulation of the lateral canals through Lorentz force resulted in a horizontal nystagmus by the so-called vestibulo-ocular reflex (VOR). The VOR normally serves to stabilize an image on the retina in case of head movements (Roberts et al. 2011). The direction of the nystagmus was dependent on orientation of the field lines and angle of the head. Inducing additional TVMF by moving the scanner bed did not change the (magnitude of) findings. Further evidence for a working mechanism by static magnetic field induced Lorentz forces on the VOR came from computer modelling (Antunes et al. 2012; Glover et al. 2014) and experimental studies with lesioned animals (Cason et al. 2009), healthy volunteers (Mian et al. 2013) and patients (Roberts et al. 2011; Ward et al. 2014a).

Based on recently designed models (Antunes et al. 2012), cupular pressure difference is supposed to be around 0.23 mPa when lying in the bore in a 1.0 T SMF. This is expected to result in a very small 1.4 degree/sec horizontal slow phase velocity upon stimulation of predominantly lateral canals. Although the subjects in our experiment were exposed to these field strengths, the orientation of the semi-circular canals to the magnetic field lines was different. Subjects sat or stood upright in front of the MRI bore since we aimed to mimic occupational exposure of health care workers near an MRI system. In an upright sitting or standing position stimulation of the lateral canals by Lorentz forces is supposed to be stronger than in lying position (Roberts et al. 2011).

Moreover, also the performance of head movements will have induced cupular deflections per se, and will have resulted in much higher eye velocities. This might have masked a very small nystagmus as induced by the relatively small Lorentz

induced pressure changes. Based on our findings we conclude that a 1.0 T SMF induced Lorentz force in the lateral canals is likely too low to result in a detectable horizontal nystagmus.

Deflection of the cupula by SMF induced Lorentz forces can probably also play a substantial role in oculomotor functions, postural stability and cognitive abilities related to the visuomotor performance and spatial orientation, since there is a direct connection from vestibular nuclei to eye muscles, spinal cord and cortical areas in the brain involved in cognitive functioning (Angelaki et al. 2008). Effects of SMF exposure on oculomotor performance have not been reported before. Although, disturbed oculomotor functions were demonstrated when exposed to the stray SMF in our experiment (van Nierop et al. submitted-b), we reason that the induced Lorentz forces were too weak to explain this change in saccadic eye velocity. Moreover, saccadic eye movements are not mediated by vestibular nuclei in the brain (Carpenter 1991).

Evidence for a mediating role of the vestibular organ in magnetic field induced postural instability comes from animal research where zebra fish displayed rolling behavior when exposed to SMF > 4.7 T (Ward et al. 2014b).

Vestibular mediated changes in cognitive functions are not likely at field strengths of 1.0 T since decreased verbal memory was only revealed when exposed to the combination of SMF+TVMF rather than to the SMF alone. Other studies showed that healthy volunteers within the homogeneous SMF of a scanner bore did not demonstrate cognitive changes when exposed up to 9.4 T SMF (Atkinson et al. 2010; Chakeres et al. 2003; Gilles et al. 2013; Heinrich et al. 2013; Lepsien et al. 2012). Therefore, it remains debatable whether magnetic field induced Lorentz forces in the SSC could solely explain the behavioral changes as found in the stray SMF. We hypothesize that in a 1.0 T stray SMF at most an additive or mediating role of the vestibular organ through one of the other mechanisms is more plausible, e.g. sensory conflict/ weighting theory or processing capacity theory.

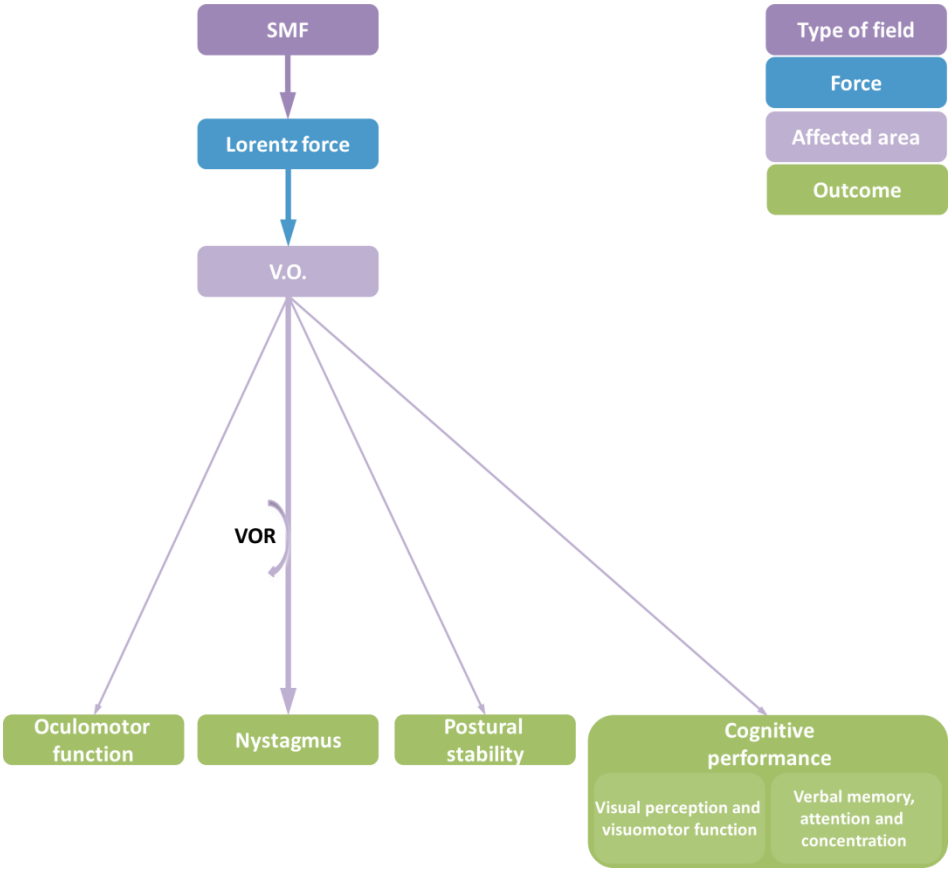

Figure 2 Proposed working mechanisms of SMF induced Lorentz forces on the vestibular organ and suggested behavioral responses regarding oculomotor function, nystagmus, postural stability and of cognitive performance.
Thick lines indicate most likely pathways of action. Thin lines indicate possible action pathways. Abbreviations: SMF, static magnetic field; V.O., vestibular organ (as target organ of the vestibular system); VOR, vestibular-ocular reflex.

Electromagnetic induction

Electromagnetic induction is the mechanism by which a changing magnetic field generates an electrical field in a conductor, also known as Faraday's Law. Performing head movements within a stray SMF as in our experiments will have generated electrical currents in the brain, see Figure 3. The induced electrical fields are difficult to estimate exactly, but based on computational models an electrical field between 0.5 and 2 V/m could be reached in front of a 4 T scanner when moving at 1 m/s (Crozier et al. 2005), or 0.13 V/m for the inner ear when in a 1.0 T SMF and 1.0

T/s TVMF (Laakso et al. 2013). Higher fields or faster movement will induce stronger electrical fields. Based on these models, in our experiment a 1.0 T SMF with 2.4 T/s TVMF will probably induce electrical fields exceeding 0.13 V/m in the inner ear and cortical areas.

This induced electrical current is well above the 15 mV needed for membrane depolarization of a neuron, which can therefore enable or disable the generation of an action potential. In this way the induced electrical currents can lead to neuron modulation and (inhibition of) neurotransmitter release. Electrical stimulation has been shown to interfere with neuron activity, resulting in changed cortical rhythms and cognitive functions (see for review (Herrmann et al. 2013)). The electrical currents as induced in our MRI experiments could have had a very random pattern due to small body and head motions during task performance. In contrast, a relatively smooth sinus pattern is induced during standardized head movements before every single task with a frequency of 0.6 Hz. These movements are supposed to induce an electromagnetic field in the same slow frequency range (Marshall et al. 2013), but can also modulate the amplitude of higher frequency oscillations (Reato et al. 2013). The physiological parameters of electromagnetic induction are multitudinous with regard to stimulus characteristics and neuronal network dynamics. Major parameters seem to be frequency, intensity, and phase of stimulation (Antal et al. 2013). Moreover, the effect is nonlinearly related to stimulation intensity and can sometimes be inhibitory (low intensity stimulation), have no net effect (intermediate stimulation intensity) or have an excitatory effect (strong stimulation intensity) (Berger et al. 2011; Moliadze et al. 2012).

Movement induced electromagnetic induction in the magnetic fields of an MRI does not target specific brain areas, cognitive domains or functions. This might explain the diversity of the affected tasks and functions shown in the experiments. Still, this appears not to be the most plausible mechanism since no cognitive changes were observed with induced currents as raised by the movement of subjects into the bore in supine position up to 7.0 T and maximal 0.8 T/s (Heinrich et al. 2013). We suggest that electromagnetic induction induced by a 2.4 T/s TVMF is at most an additive mechanism in e.g. influencing information processing capacity.

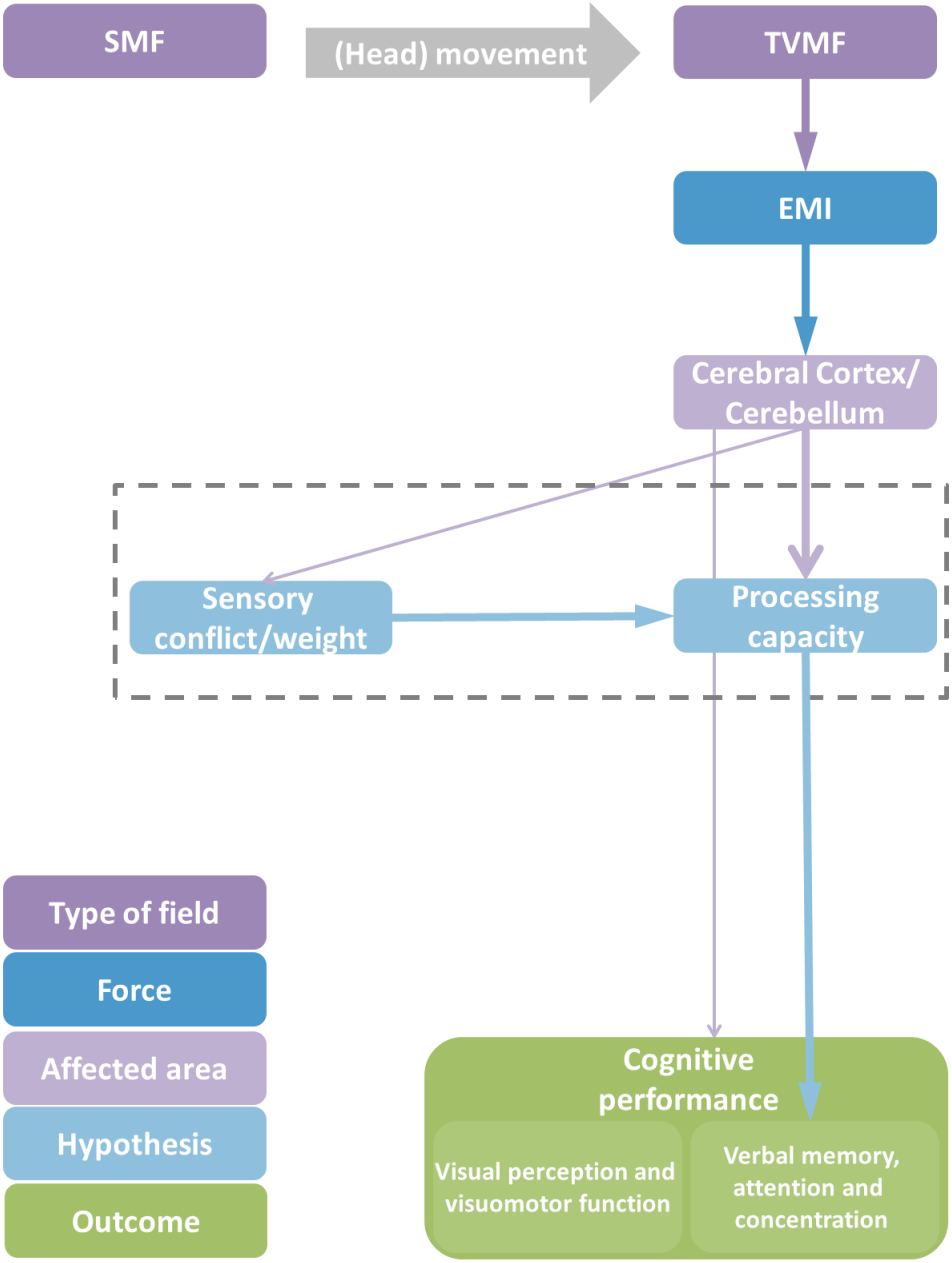

Figure 3 Proposed working mechanisms of time-varying magnetic field (TVMF) induced electromagnetic induction on cognitive performance. Thick arrows indicate most likely pathways of action. Thin arrows indicate possible action pathways. Broken line box includes hypotheses of possible mediating mechanisms. Abbreviations: SMF, static magnetic field; TVMF, time-varying magnetic field; EMI, electromagnetic induction.

Sensory conflict or sensory weighting theory

Senses often receive information that is analogous, but sometimes information is conflicting as suggested in motion sickness. Here, the most accepted theory is that a mismatch occurs between perceived visual, vestibular and proprioceptive information (Reason et al. 1975) or between the observed and expected signals from these senses (Bles et al. 2000). Within the magnetic fields in the scanner room a mismatch could occur when perceived visual information, (whether or not during head movements), vestibular information (stimulation by magnetic field induced Lorentz forces) and proprioceptive information does not correspond, see Figure 4. For example, the performance of head movements in a motion sickness provocative environment is known to enhance motion sickness (Bles et al. 2000). The kind of reported transient and subtle sensory symptoms of nausea, vertigo and dizziness in stray magnetic fields (Schenck 1992) resemble to core symptoms of motion sickness (Graybiel et al. 1968). Furthermore, decreased postural control (Bles et al. 2000) and cognitive functions (Cowings et al. 2001; Golding et al. 1992; Gresty et al. 2008; Muth et al. 2006; Paule et al. 2004) of especially spatial orientation, are also associated with the experience of disorientation and motion sickness (Bos et al. 1998). Therefore, the decreased cognitive performance and postural instability as demonstrated in our MRI experiments could at least in theory be caused by conflicting sensory information.

Another possibility is that during SMF (and TVMF) exposure, the relative weight the brain puts to bottom up information is shifted towards the received vestibular information, thereby suppressing e.g. visual input. It has been demonstrated that vestibular afferents project to multisensory vestibular cortex areas where interactions with other cortical areas occurs (zu Eulenburg et al. 2012). E.g. a visual-vestibular interaction was found in imaging studies where vestibular stimulation activated the related parieto-insular vestibular cortex (PIVC) and deactivated the occipital visual cortex, and the other way around when visual cortex was stimulated (Brandt et al. 1998; Brandt et al. 2002; Wenzel et al. 1996). This inhibitory reciprocal visual-vestibular interaction prevents from a mismatch between sensory information by shifting the sensory weight (Dieterich et al. 2000). It might be that the shifted sensory attention towards the strongest perceived (vestibular) bottom up information input resulted in a decreased performance related to the visual (and probably other) domains as demonstrated in our MRI experiments.

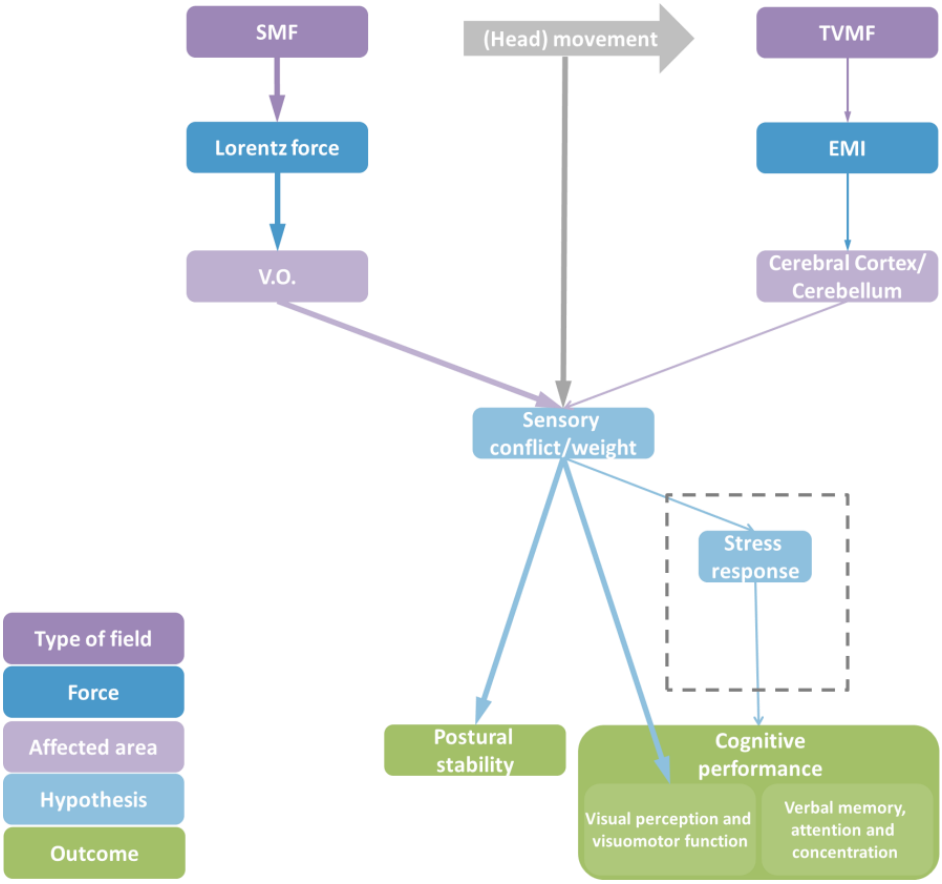

Figure 4 Proposed working mechanism of sensory conflict/ sensory weighting by exposure to static (SMF) and time-varying magnetic fields (TVMF) on behavioral measures of postural stability and cognitive performance. Thick lines indicate most likely pathways of action. Thin lines indicate possible action pathways. Broken line box includes a hypothesis of a possible related mechanism. Abbreviations: SMF, static magnetic field; TVMF, time-varying magnetic field; EMI, electromagnetic induction; V.O., vestibular organ (as target organ of the vestibular system).

A related mechanism to sensory conflict/ sensory weighting theory is that of an acute biological stress response in the body. Exposure to strong (time-varying) magnetic fields is an experience to which our body is not accustomed to. This does not necessarily lead to the perception of stress but could result in an acute physiological stress response as such. Stress could then increase the level of catecholamine's in the brain in turn affecting the prefrontal cortex and working memory functions (Liston et al. 2009; Qin et al. 2009). Moreover, the possible

mismatch of visual, vestibular and proprioceptive information when performing head movements in a magnetic field could induce a stress response resulting, among others, in increased levels of cortisol (adrenocorticotrophic hormone, HPA axis), prolactin, and ACTH (Drummer et al. 1990; Eversmann et al. 1978; Otto et al. 2006; Schneider et al. 2007). Especially the glucocorticoid cortisol might modulate cognitive functions in the frontal lobe and hippocampus, depending on the circulating levels (see for review (Lupien et al. 2007)). Elevated cortisol levels were shown in humans directly following MRI scans (Eatough et al. 2009; Tessner et al. 2006), but they decreased when the individuals were repeatedly exposed (Peters et al. 2011). There is a large individual difference in perception and resistance to stress and motion sickness, therefore the release of, and response to, stress hormones is known to be highly variable between individuals (Bles et al. 2000; Lupien et al. 2007). A biological stress mechanism is however not the most conceivable pathway because it was shown that (movement in supine position in the) homogeneous SMF up to 7 T and 0.8 T/s did not affect cortisol, epinephrine and norepinephrine levels (Gilles et al. 2013). When stress hormones are released after exposure to strong magnetic fields, we expect cognitive performance to be modulated, especially on tasks requiring a high working memory load.

A modulating factor within the sensory conflict theories could be susceptibility to motion sickness. Motion sickness susceptibility as a designation for e.g. sensory conflicting information is difficult to assess. Many techniques have been used to test susceptibility for different motion sickness provocative situations without too much success (Miller et al. 1970; Miller et al. 1972). The susceptibility measures we used correlated very poorly with subjective sensitivity to motion sickness (Van Nierop et al. submitted-a). To take possible modulating effects into account, we used subjective sensitivity to motion sickness as a selection criterion in our experiments (see appendix 1 for distribution over experiments) and adjusted analyses for severity of motion sickness. In our second experiment we tried to relate test performance to responsiveness of the vestibular organ. Subjective sensitivity to motion sickness and objective vestibular responsiveness on the caloric reflex test and rotary chair test were not found to modulate test performance as observed in the stray magnetic fields of the MRI.

Information processing capacity

Another mechanism that may be important in explaining magnetic field induced cognitive changes is the capacity to process information (Miller 1956). The capacity of the processing system is dependent on dimensions (e.g. for visual stimuli: color, size, brightness, and position) and amount of variables of the stimuli, commonly expressed in units, bits or chunks. An increasing amount of bottom up information received by the senses will increase the amount of information to be processed, up to a certain level. Then the processed information will level off, and by doing, so define the maximum processing capacity (Eriksen et al. 1955; Hake et al. 1951). When even more bottom up information is added, the accuracy per se reduces, which will result in increased response times or higher error rates (Eriksen 1955; Miller 1956). It is difficult to define at which point the maximum capacity is reached for each individual since the amount of information is a dimensionless quantity (Miller 1956).

A good candidate system with features of processing capacity is the working memory system, which integrates processes, and disposes and retrieves information in order to act. A model designed by Baddeley and Hitch (Baddeley 2000; Baddeley 1974) proposes that the central executive is responsible for directing attention to relevant information and coordinating cognitive processes when multiple tasks are performed simultaneously in ongoing activity.

When considering that magnetic field exposure (un)consciously activates senses (e.g. vestibular organ and taste), parts of the processing capacity will be engaged with handling this information, see Figure 5. Performance of head movements within the magnetic fields results in electromagnetic induction, and in some subjects also transient, light sensory symptoms of nausea and dizziness, in addition to the visual input by the moving head and stimulated vestibular organs. As a consequence, even more capacity is needed to process this information. When at this point a task is performed requiring a high cognitive demand, an overflow of information reaches the processing system. In this way, task performance on a broad range of tasks requiring a high cognitive demand could be influenced. The test battery as applied showed, among others, the complex and inhibition reaction time task were tasks that tap working memory in terms of processing capacity and showed an effect of exposure. Individual differences in processing capacity will define the ability to control information (Fukuda et al. 2009) and could explain the differences

in test performance between individuals when exposed. The larger an individual's processing capacity, the better he or she will be able to control his or her attention.

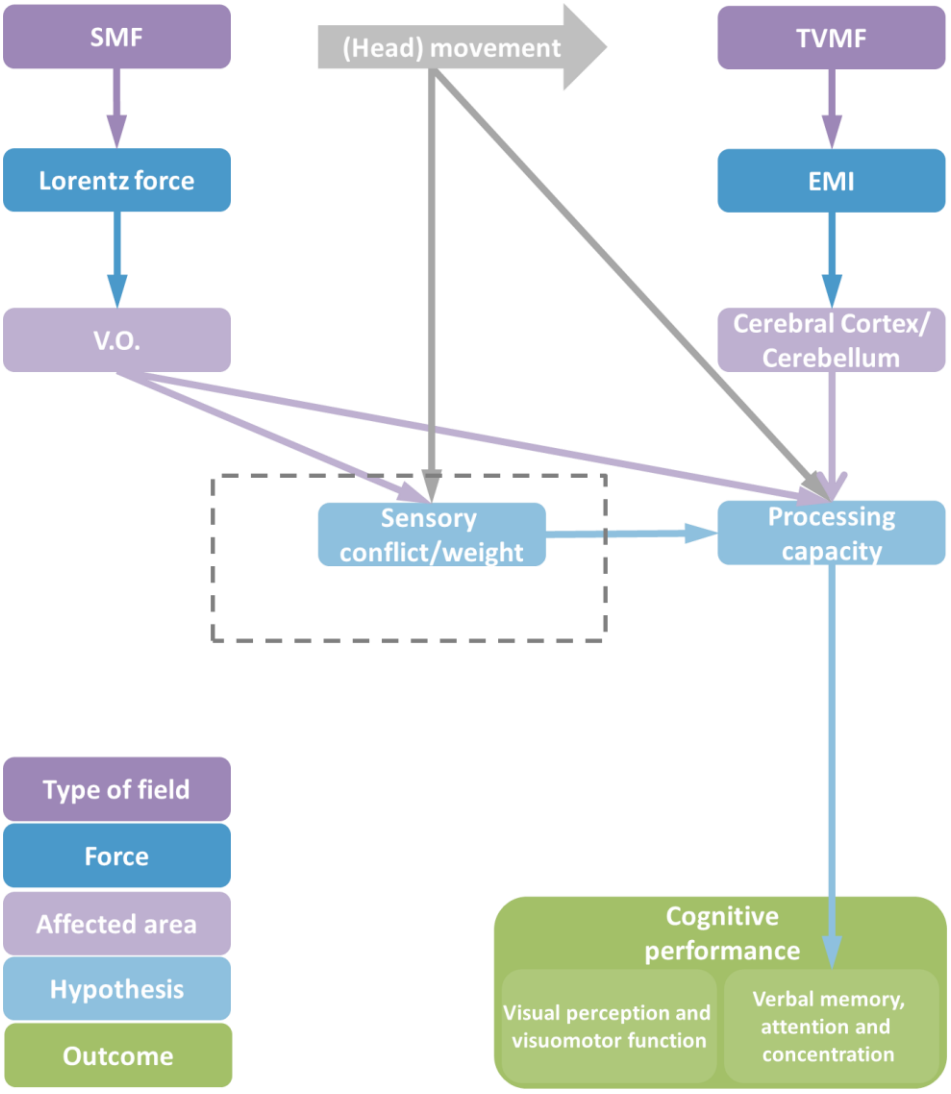

Figure 5 Proposed working mechanisms of processing capacity by exposure to static (SMF) and time-varying magnetic fields (TVMF) on behavioral measures of cognitive performance. Thick lines indicate most likely pathways of action. Thin lines indicate possible action pathways. Broken line box includes a hypothesis of a possible interaction mechanism. Abbreviations: SMF, static magnetic field; TVMF, time-varying magnetic field; EMI, electromagnetic induction; V.O., vestibular organ (as target organ of the vestibular system).

Suggested working mechanisms

Although highly speculative, we try to underline the most likely mechanism given the absence of cognitive changes in a homogeneous SMF up to 9.4 T (Atkinson et al. 2010; Chakeres et al. 2003; Gilles et al. 2013; Heinrich et al. 2013; Lepsien et al. 2012) together with the observed cognitive changes in lower inhomogeneous stray SMF of 1.0 T and movement induced TVMF of 2.4 T/s (de Vocht et al. 2007; de Vocht et al. 2006; de Vocht et al. 2003; van Nierop et al. 2014; van Nierop et al. 2012). We hypothesize that the presented behavioral changes have not been induced by a single mechanism, but that several mechanisms play a role or interact, see Figure 1.

For the induced cognitive changes of attention and concentration, and verbal memory, the processing capacity seems to be the limiting factor. Whether and how electromagnetic induction and sensory conflict/weighting could play a role or influence the processing capacity is unclear. It is however clear that from a lot of different modalities (e.g. V.O. stimulation, perceived sensory information, EMI, head movements, conflicting information), information has to be processed. Which modality is decisive in reaching the limit remains unclear.

Cognitive tasks related to visual perception and visuomotor functions seem most likely influenced by sensory weighting of information. A shift in attention towards SMF induced vestibular stimulation, possibly together with head movement induced vestibular/visual stimulation, will result in less attention and concentration for tasks requiring visual, spatial, and motor performance.

In contrast, postural instability as observed in the stray magnetic field together with movement induced TVMF seems to have an underlying mechanism that is driven by SMF induced Lorentz forces in the vestibular organ. Moreover, postural instability is possibly enhanced by the performance of head movements resulting in conflicting information and/or dizziness.

The change in oculomotor function of saccadic velocity has to be replicated before an underlying mechanism can be exactly hypothesized. At this moment we suggest that the dipole moment of the eye in a magnetic field is the most plausible explanation for the increase in velocity to the right and left side. At higher field strengths a modulating effect of magnetic field induced Lorentz forces in the semicircular canals could be possible.

Future prospects

To find further evidence for working mechanism(s) underlying the variety of behavioral changes due to SMF and TVMF exposure as described in this thesis, the presented theories should be used as a starting point.

The Lorentz induced vestibular component underlying nystagmus could be further explored by assessing nystagmus not only in the homogeneous SMF but also in the stray fields of the scanner at field strengths above 1.0 T. Positioning of subjects at different postural orientations with respect to the magnetic field lines would provide more insight into which SCC contributes to the largest behavioral responses. The influence and consequences of individual differences in morphology of the vestibular organ can be defined by MR Imaging. Since it is proven that the SMF induced Lorentz forces change firing rates of the SSC(s), it would be of interest whether vestibular related functions are also affected. For instance the change in postural stability needs to be further investigated since a direct influence of vestibular disturbance seems possible (van Nierop et al. 2013; Ward et al. 2014b). Associated functions of oculomotor performance can be assessed in healthy volunteers, preferably when in the homogeneous fields of a 7 T MRI system. In addition, the effects of stray magnetic fields on saccadic eye movements also have to be replicated, preferably by use of MRI compatible video-oculography. Different orientations of the eyes with regard to the field lines could provide information about an interaction of the magnetic field with the dipole moment of the eye. In these settings, patients lacking vestibular function could act as a negative control group, not only for VOR induced nystagmus but also for postural assessment, oculomotor functioning and cognitive performance.

Finding further evidence for the potential role of electromagnetic induction and the ability to modulate neuron communication will be harder to achieve. Results of cell culture studies are difficult to extrapolate into an integrated neuronal network predicting behavioral outcomes. Also whole brain stimulation by other techniques, e.g. by transcranial alternating current stimulation, are only of limited value for this purpose. To see whether specific brain areas are influenced by magnetic fields or head movement induced TVMF, an electroencephalogram (EEG) could be recorded. However, this needs an MRI compatible EEG device and would provide only limited information about functionality of the domains because of low spatial sensitivity.

The role of the processing capacity in magnetic field induced behavioral changes could be tested by adding even more information dimensions during magnetic field exposure until the maximum capacity of the processing system is reached. As a result, a more robust response should be visible even on relatively simple cognitive tasks. Alternatively, an equivalent for the amount of occupied capacity by magnetic field exposure could be defined by adding more information dimensions, when testing outside of the magnetic field, until a similar decreased test performance is found as during magnetic field exposure. Moreover, also patients with a reduced processing capacity (e.g. working memory capacity) could be tested in a sham controlled exposure setting to explore whether their performance is more easily and strongly affected.

A stratified analysis of subjects, based on reported sensory symptoms in the magnetic field, could be performed to reveal possible differences in test performance between groups. In this way an indication for a mechanism by sensory conflict, sensory weighting or magnetic field susceptibility could be explored. In our experiments this analysis was not possible because of the small group sizes, as only around 30% of the subjects reported symptoms (except from metallic taste) in the exposure condition (and not in the sham condition).

In general, with the use of higher field strengths above 1.0 Tesla a larger behavioral response is expected as well as an increasing number of subjects reporting sensory symptoms. This makes it easier to investigate the working mechanisms as proposed. Moreover, an exposure-response relationship could be more easily established.

Furthermore, the demonstrated differences in test performance on a postural stability task in subjects with vestibular unilateral weakness could be further elaborated and confirmed in a group with higher contrast in unilateral weakness or patients suffering from unilateral weakness.

The experimental test battery could also be improved by the development of an MRI compatible computerized neuropsychological test system. Such a test battery would help to realize uniform administering protocols, improve accuracy of assessments and standardize scoring protocols and decisions rules.

Conclusion

In the experiments described in this thesis it has been demonstrated that exposure to a 1.0 T stray SMF of an MRI scanner in stand-by modus modulates oculomotor function, while performance of head movements inducing an additional TVMF of 2.4 T/s resulted in postural instability and decreased cognitive functions of visuomotor function and visuoperception, verbal memory, and attention and concentration. Indications for a working mechanism via the vestibular system explaining the magnetic field induced behavioral changes could not be confirmed with certainty but could also not be ruled out. Responsiveness of the vestibular system did not modify cognitive and oculomotor changes. However, an indication for a modified postural stability was found for subjects with vestibular unilateral weakness when exposed to stray SMF and motion induced TVMF. Direct stimulation of the vestibular system with GVS did not result in a behavioral response pattern which resembled the pattern as found during exposure to MRI-related stray magnetic fields.

The results of these studies strongly suggest that the combination of exposure to SMF, TVMF and the performance of head movements are required to induce cognitive and postural changes, which points in the direction of certain proposed working mechanisms. The affected cognitive functions do not seem specific for one domain but are merely related to total level of cognitive capacity required. The capacity required to process vestibular, sensory and visual information and to perform tasks that largely call on working memory, possibly leads to an overflow of information that can be processed simultaneously. Changed cognitive functions of visuoperception and visuomotor performance might more likely result from an attentional shift between vestibular, proprioceptive and visual information as described in the sensory conflict and sensory weighting theory. Tasks that demand vestibular, sensory and visual information can be impaired due to conflicting information received or a shift in attention towards one of these modalities. When the essential vestibular information is modified by magnetic field induced Lorentz force in the SSC, this affects visual (motor) functions and possibly also postural stability. The observed changes in oculomotor function need to be confirmed first. Nevertheless, a mechanism of SMF forces working on the dipole moment of the eye seems plausible at least in theory.

The magnitude of change in behavioral performance associated with a magnetic field of 1.0 T and 2.4 T/s is small but significant. Given the trend of scanning at ultrahigh field strengths of 7 T and higher, the exposure of personnel working with and around MRI scanners is supposed to increase in the coming years. This can have serious consequences, especially for those who need to maintain a high level of precision and concentration, e.g. surgeons performing MRI-guided operations. Therefore, the knowledge as presented in this thesis should among others be used to design relevant control measures to lower exposure and reduce the occurrence of behavioral changes for individuals employed under these conditions.

Appendix Table 1 Score on the short version of the motion sickness questionnaire (Golding 1998) and classification of the subject population in experiment MRI 1 (van Nierop et al. 2013; van Nierop et al. 2012) (N=30) and MRI 2 (van Nierop et al. submitted-b; van Nierop et al. 2014) (N=36) and GVS experiment (Van Nierop submitted) (N=30)

Classification of sensitivity	MSSQ	Experiment		
		MRI 1	MRI 2	GVS
	score	# Subjects	# Subjects	# Subjects
Low	3	15	10	10
Medium	4	5	7	5
	5	9	10	9
	6	1	5	5
high	7	0	2	1
	8	0	1	0
	9	0	1	0
Total Subjects		30	36	30

Classification to low, medium and high sensitivity to motion sickness as adjusted for in mixed model.

Sensitivity to motion sickness was defined as a sum score for three types of symptoms in last 10 years (general sensitivity, nausea and puking) on a four-point Likert scale ranging from one (not at all) to four (very often). Total MSSQ score ranged between 3 and 12 points.

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List of abbreviations

AIC	Akaike Information Criterion
AC	Alternating Current
AM	Arithmetic mean
CTA	Conditioned Taste Aversion
CT	Computed Tomography
DC	Direct Current
EMF	Electro Magnetic Field
fMRI	Functional Magnetic Resonance Imaging
GM	Geometric Mean
GVS	Galvanic Vestibular Stimulation
ICNIRP	International Commission on Non-Ionizing Radiation Protection
MF	Magnetic Field
MFIV	Magnetic Field Induced Vertigo
MHD	Magnetohydrodynamic
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
RF	Radio Frequency
SCC	Semicircular canal
SD	Standard deviation
SMF	Static Magnetic Field
T	Tesla (1 Tesla = 10000 Gauss)
TMS	Transcranial Magnetic Stimulation
TVMF	Time-varying Magnetic Field
VOR	Vestibulo-ocular reflex

Units

Magnetic field strength (H)	in	Ampere per meter	A/m
Magnetic flux (X)	in	Weber	($1x10^8$ field lines)
Magnetic flux density (B)	in	Tesla	T ($1Wb/m^2$)
		Gauss	G ($1x10^{-4}T$)
Electric field strength (E)	in	Volt per meter	V/m
Static magnetic field (B_0)	in	Tesla	T
Gradient field	in	Tesla per meter	T/m
Time-varying magnetic field	in	Tesla per second	T/s
Frequency	in	Hertz	Hz
Electric current	in	Ampere	A

Summary

The growing popularity of MRI in clinical settings and the innovative applications in e.g. MRI guided surgery has resulted in more frequent, longer and higher levels of exposure to the stray magnetic fields for employees. Especially the use of stronger field strengths in MRI has been associated with unwanted sensory stimulation and difficulties in task performance. These induced side effects have heightened the need to further explore the biological and health effects of exposure to strong MRI-related magnetic fields. This thesis focuses on identifying the effects of exposure to stray static magnetic fields (SMF) and movement-induced low-frequency time-varying magnetic fields (TVMF) on behavioral changes in cognitive functions and vestibular related functions of postural stability and oculomotor performance and to unravel underlying mechanisms. Three objectives have been addressed:

I. Explore behavioral domains and functions affected by SMF and TVMF exposure

To enable an overview it was essential to identify and map behavioral functions that could be affected when exposed to MRI-related stray magnetic fields. Healthy volunteers exposed to the stray magnetic fields of a 7 Tesla MRI scanner in combination with head movement-induced TVMF showed a decreased eye-hand coordination, spatial orientation, attention and concentration (Chapter 2), visual acuity and verbal memory (Chapter 4). Affected vestibular related functions included decreased postural stability (Chapter 5) and change in oculomotor function of saccadic velocity (Chapter 6). Although current and previous studies do not exactly show similar behavioral tasks to be affected, exposure to (time-varying) static magnetic fields does often seem to decrease cognitive and vestibular related performance per se. In particular domains including attention and concentration, verbal memory and visual related functions like visuomotor performance and postural stability have been repeatedly identified.

II. Disentangle the effects from exposure to SMF and TVMF

So far, all identified behavioral changes occurred when exposed to a combination of stray SMF and low-frequency head movement-induced TVMF. Since stray magnet fields are always present around an MRI system in stand-by modus, we could only make a distinction between effects resulting from exposure to SMF only and from

exposure to a combination of SMF and movement-induced TVMF. Therefore, test performance in the SMF only and SMF+TVMF conditions have been compared to corresponding sham conditions, e.g. with and without head movements. From all assessed tasks only the decrease in verbal memory could be attributed to the combination of SMF and TVMF rather than exposure to SMF alone (Chapter 4). Moreover, the change in saccadic velocity seemed to be determined by exposure to SMF as such rather than by a combination of SMF+TVMF (Chapter 6). Other earlier identified cognitive functions were not affected in the SMF nor in the SMF+TVMF exposure condition of this experiment.

III. Indications for a working mechanism; involvement of the vestibular system

For some of the reported sensory symptoms a mediating role for the vestibular system has been suggested. Therefore, a mediating role for the vestibular system underlying the magnetic field induced behavioral changes was investigated through two different approaches.

-**Responsiveness of the vestibular system** was investigated in relation to performance within MRI-related magnetic fields (Chapter 7). Subjects were classified based on several measures representing vestibular responsiveness (e.g. subjective sensitivity to motion sickness, responsiveness to low and medium-frequency movements and unilateral weakness). None of the low and high vestibular responsiveness groups showed a stronger response on cognitive tasks or oculomotor functions when exposed to magnetic fields. However, a modifying effect of vestibular unilateral weakness was demonstrated on postural stability following exposure to SMF+TVMF. Subjects with high unilateral weakness showed an improved postural stability when performing head movements in the SMF. It was hypothesized that these subjects might use the magnetic fields as an orientation frame for the control of body movement. Given the small group sizes these findings should be seen as preliminary and will need replication. We do hypothesize however that vestibular responsiveness does not seem to be a good predictor for test performance on cognitive and vestibular related tasks in stray magnetic fields from a 7-T MRI system.

-Test performance after **Controlled stimulation of the vestibular system** by Galvanic Vestibular Stimulation (GVS) was compared to test performance in MRI-related magnetic fields on similar tasks (Chapter 8). The behavioral response pattern on

cognitive, postural and oculomotor tasks after GVS did not resemble those after exposure to an MRI-related stray magnetic field. Therefore, we cannot confirm nor exclude that the vestibular system plays a (mediating) role in MRI-related magnetic field induced behavioral changes.

To underline a path of action behind the presented behavioral changes several mechanisms have been discussed. The most important underlying mechanisms include; magnetic field induced Lorentz forces in the vestibular organ, movement-induced electromagnetic induction when present in the magnetic fields, sensory conflict or sensory weighting theory between received visual and vestibular information, and limited information processing capacity following an overflow of information to be processed. Modulating factors within these theories could be an induced biological stress response and sensitivity to motion sickness.

Based on our findings we suggest that the working mechanisms underlying cognitive and postural changes strongly point towards a combination of exposure to SMF, TVMF and performance of head movements. The affected cognitive functions do not seem specific for one domain, but merely rely on the total level of cognitive capacity required. The capacity required to process vestibular, sensory, and visual information, and perform tasks who require working memory possibly leads to an overflow of information that can no longer be processed simultaneously.

Changed cognitive functions of spatial orientation and visuomotor performance might more likely result from an attentional shift between vestibular, proprioceptive and visual information as described in the sensory conflict and sensory weighting theories.

Tasks that demand on vestibular, sensory and visual information can be affected due to conflicting information received or a shift in attention towards one of these modalities. When the essential vestibular information is modified by magnetic field induced Lorentz force in the semicircular canals this might affect visuo(motor) functions and possibly also postural stability.

Changes in oculomotor function need to be replicated in independent experiments. Nevertheless, a mechanism by SMF forces working on the dipole moment of the eye seems plausible.

In conclusion, the magnitude of the found changes in behavioral performance by magnetic field of 1.0 T and 2.4 T/s is small but of serious significance. Given the trend of scanning at ultrahigh field strengths (7 T and higher) exposure of personnel working with and around MRI scanners is supposed to further increase in the coming years. This can have serious consequences for employees, and especially for those employees who need to maintain a high level of precision and concentration e.g. surgeons performing MRI guided operations. Therefore, the knowledge as presented in this thesis should among others be used as a basis for the design of relevant control measures and policies to lower exposure and reduce the occurrence of behavioral changes for individuals employed under these conditions.

Samenvatting

De populariteit van Magnetische resonantie imaging (MRI) is grotendeels te danken aan de vele toepassingsmogelijkheden; naast de beeldvorming van lichaamsstructuren kunnen ook dynamische processen in de hersenen worden vastgelegd of operaties worden uitgevoerd met behulp van MRI. Dit heeft geresulteerd in een toename in gebruik van MRI waardoor personeel frequenter wordt blootgesteld aan verschillende vormen van magnetische strooivelden in de scanner ruimte. Om de verschillende toepassingsmogelijkheden te faciliteren is de intensiteit van de magneten sterker geworden over de jaren. Het gevolg hiervan is dat de ultra-sterke magneten (>1.5 Tesla) van de scanner niet meer uit geschakeld worden en de scanner altijd in stand-by modus blijft, waardoor de statische magnetisch strooivelden altijd aanwezig zijn. Deze ontwikkelingen tezamen zorgen ervoor dat personeel vaker en hoger wordt blootgesteld aan deze magneetvelden.

Personeel en patiënten die in en rondom de scanner aanwezig zijn, worden blootgesteld aan de magneetvelden. Sommigen ervaren dan symptomen zoals misselijkheid, duizeligheid en een metaalsmaak. Daarnaast zijn er experimentele aanwijzingen dat ook tijdelijk subtiele veranderingen optreden in uitvoerende functies, zoals de fijne motoriek en concentratie. Deze aanwijzingen onderstrepen de noodzaak om de biologische en eventuele gezondheidseffecten van blootstelling aan MRI-gerelateerde magneetvelden verder te onderzoeken. Dit proefschrift richt zich op het identificeren van veranderingen in het functioneren van de hersenen en het evenwichtssysteem (vestibulair systeem) bij blootstelling aan statische magneet velden (SMF) en door beweging geïnduceerde laagfrequente tijdsafhankelijke magneetvelden (TVMF). Hierbij wordt specifiek gekeken naar cognitieve en vestibulair (evenwichts-) gerelateerde functies. Daarnaast proberen we voor de gevonden effecten mogelijke onderliggende werkingsmechanismen te achterhalen. Drie doelstellingen worden behandeld:

I. Het identificeren van functies die beïnvloedt worden door blootstelling aan SMF en TVMF

Om een beeld te krijgen welke operationele functies beïnvloed worden bij blootstelling aan MRI-gerelateerde magneetvelden hebben we een uitgebreide experimentele test batterij samengesteld. Hierin zijn taken opgenomen voor cognitieve domeinen en vestibulaire functies die belangrijk zijn bij het uitvoeren van

taken die een grote concentratie en veel precisie vergen zoals ook nodig is bij het uitvoeren van medische operaties in de magneetvelden van een MRI scanner. In twee experimentele studies zijn gezonde vrijwilligers blootgesteld aan de magnetische strooivelden van een 7 Tesla MRI-scanner in combinatie met TVMF die opgewekt werden door standaard hoofdbewegingen. Oog-hand coördinatie, ruimtelijke oriëntatie, aandacht en concentratie verminderen (hoofdstuk 2) na blootstelling aan de combinatie van SMF en TVMF magneetvelden, evenals zichtscherpte en het verbale geheugen (hoofdstuk 4). Op vestibulair gerelateerde functies liet men bij blootstelling aan magneetvelden een verminderd houdingsevenwicht zien (hoofdstuk 5) en een veranderde snelheid van sprongsgewijze oogbewegingen (saccades) (hoofdstuk 6). In eerdere studies en onze studies zijn op een aantal domeinen herhaaldelijk veranderde testprestatie gevonden, te weten: aandacht en concentratie, verbaal geheugen en visueel gerelateerde functies als oog-hand coördinatie en houdingsevenwicht. Hoewel niet precies dezelfde taken beïnvloed werden, lijkt blootstelling aan SMF+TVMF cognitieve en vestibulair gerelateerde prestaties dus te verlagen.

II. Onderscheid tussen de effecten van blootstelling aan SMF en TVMF

Tot nu toe zijn alle geïdentificeerde veranderingen in testprestaties aangetoond bij blootstelling aan de combinatie van strooi SMF en hoofdbeweging geïnduceerde TVMF. Omdat de strooi magneetvelden altijd aanwezig zijn rondom een MRI scanner in stand-by modus, kunnen we in onze experimentele aanpak alleen onderscheid maken tussen effecten van blootstelling aan SMF alleen en van blootstelling aan de combinatie van SMF en TVMF. We hebben daarom de test prestatie in het SMF en de combinatie van SMF en TVMF vergeleken met corresponderende controle condities, n.l. respectievelijk zonder en met de standaard hoofdbewegingen voorafgaand aan elke test. Het verbaal geheugen was verminderd in de SMF+TVMF blootstellingsconditie, waardoor dit waarschijnlijk kan worden toegeschreven aan de combinatie van SMF+TVMF blootstelling in plaats van blootstelling aan SMF alleen (Hoofdstuk 4). Een veranderde snelheid van sprongsgewijze oogbewegingen bij blootstelling lijkt te worden bepaald door blootstelling aan SMF alleen en niet door de combinatie van SMF en TVMF (Hoofdstuk 6). Andere, eerder geïdentificeerde cognitieve en vestibulaire functies werden niet beïnvloed in de SMF of SMF en TVMF blootstellingscondities van dit experiment.

III. Indicaties voor een werkingsmechanisme; de betrokkenheid van het vestibulair systeem

Een aantal van de sensorische symptomen die mensen in de magneetvelden bij scanners ervaren, zoals duizeligheid en misselijkheid, suggereren betrokkenheid van het vestibulair orgaan. We hebben daarom op verschillende manieren een mogelijk mediërende rol voor het vestibulair system onderzocht op de gedragsmatige veranderingen die zijn gevonden bij blootstelling aan het magneetveld.

De eerste manier om een mogelijke rol van het vestibulair systeem te bepalen, is te onderzoeken of de responsiviteit van het vestibulaire systeem de test prestatie in MRI-gerelateerde magneetvelden veranderd (Hoofdstuk 7). Gebaseerde op verschillende maten die vestibulaire responsiviteit weergeven (namelijk subjectieve gevoeligheid voor bewegingsziekten, responsiviteit voor lage- en hoog frequente beweging en labyrint asymmetrie), liet geen van de gecreëerde normaal en hoog responsieve groepen een sterkere reactie zien op de cognitieve taken of oculomotor functies wanneer blootgesteld aan magneetvelden. Daarentegen, werd een modificerend effect van vestibulaire labyrint asymmetrie op het houdingsevenwicht aangetoond bij blootstelling aan SMF en TVMF. Een hypothese is dat deze mensen het magneetveld gebruiken als oriëntatieframe voor de controle van lichaamsbewegingen. Echter deze resultaten zullen moeten worden gerepliceerd vanwege de kleine groepsgroottes in onze studie. Desalniettemin lijkt het dat vestibulaire responsiviteit geen goede voorspeller is voor test prestatie op cognitieve en vestibulair gerelateerde taken in de strooi magneet velden van een 7 T MRI systeem.

Als directe stimulatie van het vestibulair orgaan vergelijkbare effecten teweegbrengt als gevonden in de magneetvelden, dan zou dat een onderbouwing zijn voor een werkingsmechanisme via het vestibulair systeem. De tweede manier om een vestibulair werkingsmechanisme te onderzoeken is daarom door de test prestatie na gecontroleerde stimulatie van het vestibulair systeem met Galvanische Vestibulaire Stimulatie (GVS) te vergelijken met test prestatie op gelijke taken zoals afgenomen in eerdere experimenten met blootstelling aan MRI-gerelateerde magneetvelden (Hoofdstuk 8). Het patroon in effecten op cognitieve-, balans- en oculomotor taken na GVS was niet vergelijkbaar met het patroon na bloostelling aan MRI-gerelateerde magneetvelden. We kunnen op grond hiervan daarom niet bevestigen dat het vestibulair systeem een (mediërende) rol speelt in MRI-gerelateerde magneetveld

geïnduceerde gedragsmatige veranderingen, maar een dergelijke rol is daarmee ook niet uitgesloten.

Ten derde is op grond van literatuur, experimentele bevindingen en een theoretische beschouwing meer inzicht verkregen in welke werkingsmechanisme(n) de gedragsmatige veranderingen zouden kunnen verklaren. Mogelijke mechanismen zijn 1) door magneetveld geïnduceerde Lorentz krachten in het vestibulair orgaan, 2) door beweging in het magneetveld geïnduceerde elektromagnetische inductie, 3) sensorisch conflicterende of verkeerd gewogen informatie waardoor ontvangen vestibulaire en visuele informatie niet (goed) geïnterpreteerd wordt, 4) een beperkte verwerkingscapaciteit wanneer er door magneetvelden een overvloed aan informatie door de hersenen verwerkt moet worden. Mogelijke modulerende factoren binnen deze mechanismen zijn een door de magneetvelden geïnduceerde biologische stress reactie en gevoeligheid voor bewegingsziekte zoals wagenziekte. Gebaseerd op onze bevindingen suggereren we dat de veranderingen in cognitie en houdingsevenwicht sterk wijzen naar (een) theorie(en) waarbij een combinatie van blootstelling aan SMF, TVMF en hoofdbewegingen nodig is.
De cognitieve functies die door magneetvelden beïnvloedt werden, lijken niet specifiek voor een domein maar eerder afhankelijk van de totale hoeveelheid aan cognitieve capaciteit die benodigd is. De capaciteit om vestibulaire, sensorische en visuele information te verwerken tijdens blootstelling aan magneetvelden en het gelijktijdig uitvoeren van complexe taken, leidt mogelijk tot een overvloed aan informatie die niet langer gelijktijdig verwerkt kan worden. Dit resulteert in een verminderde attentie en concentratie en verbaal geheugen, voornamelijk op taken met de hoogste moeilijkheidsgraad. De gevonden veranderingen door magneetvelden in cognitieve functies als visuele perceptie en visuomotor prestatie zijn waarschijnlijk het resultaat van een vertekende (verschoven) aandacht, waarbij een verschuiving tussen vestibulair, proprioceptie en visuele informatie plaatsvindt zoals ook omschreven is in de zintuigelijke conflict en zintuiglijke weging theorie. Taken die een beroep doen op een van deze drie informatie bronnen kunnen worden beïnvloed door conflicterende informatie of een verschuiving van aandacht naar een van de drie modaliteiten. Een mogelijke verklaring voor de verslechtering van houdinsevenwicht en mogelijk ook visuele (motor) functies is dat essentiële vestibulaire informatie wordt gemodificeerd door in het magneetveld geïnduceerde Lorentz krachten in de halfcirkelvormige kanalen van het labyrint in het vestibulair

orgaan. De gevonden veranderingen in oculomotor functie moeten eerst gerepliceerd worden in onafhankelijke experimenten. Een mechanisme waar SMF krachten werken op het dipool moment van het oog lijken hier waarschijnlijk.

Samenvattend is de grootte van de gevonden veranderingen in test prestatie in de MRI-gerelateerde strooivelden van 1.0 T en 2.4 T/s klein, maar van significante betekenis voor de praktijk. Rekening houdend met de trend van het scannen met ultra hoge veldsterktes (3 T en hoger) en nieuwe medische toepassingen zoals MRI geleide operaties, zal de blootstelling van personeel dat werkt met MRI scanners verder toenemen in de komende jaren. Dit kan gevolgen hebben voor werknemers en hun patiënten, en in het bijzonder als werknemers een hoge mate van precisie en concentratie nodig hebben zoals chirurgen die een MRI-geleide operatie uitvoeren. Daarom zou de kennis, zoals gepresenteerd in dit proefschrift, gebruikt moeten worden als basis voor het ontwerpen van relevante maatregelen die de blootstelling verlagen en het optreden van gedragsmatige veranderingen beperken voor werknemers die werken onder deze condities.

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L.E. van Nierop, Slottje P, Kromhout H, Kingma H. *MRI-related static and head movement-induced time-varying magnetic fields; nystagmus and effects on oculomotor functions and postural stability.* Submitted for publication

L.E. van Nierop, Slottje P, Kromhout H, Kingma H. *Does vestibular responsiveness modify acute effects of MRI-related magnetic fields on test performance?* Submitted for publication

L.E. van Nierop, Slottje P, Zandvoort M., Kromhout H, Kingma H. *Test performance after low-intensity galvanic vestibular stimulation compared with effects of exposure to MRI-related stray magnetic fields.* Submitted for publication

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About the author

Lotte van Nierop was born on the 24th of March 1982 in Nijmegen, the Netherlands. After graduation high school, she started laboratory education (HLO) at the Saxion Hogeschool Enschede. When the propaedeutic degree was obtained she changed plans and studied Biology at the Rijksuniversiteit Groningen (RuG). In the bachelor phase her interest shifted from growing plants to the mysterious complexity of the brain which resulted in a specialization master in cognitive and behavioural neuroscience. During the first master project at the NeuroImagingCenter (NIC) Groningen she investigated the effect of μTMS on pain perception and cognitive functions, under supervision of Dr. Ruud Kortekaas. In a second project at the department of chronobiology (RuG) she investigated the effect of different colors of light on shift work performance, under supervision of Dr. Marijke Gordijn. Because the prospective of becoming a dull researcher was still a bit frightening she followed at the same time a Master in Science communication at the same university. During her studies she worked as a student assistant for different educational classes and research projects at the institute.

After graduating in Biology and Science communication, she started in 2009 as PhD candidate in the group of Prof. Hans Kromhout at the Institute for Risk Assessment Sciences, Utrecht University. Within the Electromagnetic fields and health group she worked on a project investigating the acute behavioral effect of strong MRI related magnetic fields. The completion of this project led to the present dissertation titled 'The magnetized brain; working mechanisms for the effects of MRI-related magnetic fields on cognition, postural stability, and oculomotor function'.

Since 2015 she works as research coordinator at the ALS center, University Medical Center Utrecht. In her current position she is responsible for the coordination of international ALS-related research activities, e.g. within the Euro-MOTOR, SOPHIA, ALS-CarE and STRENGTH projects.

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Lotte