Simultaneous Exposure to MRI-Related Static and Low-Frequency Movement-Induced Time-Varying Magnetic Fields Affects Neurocognitive Performance: A Double-Blind Randomized Crossover Study

Lotte E. van Nierop,¹ Pauline Slottje,¹ Martine van Zandvoort,² and Hans Kromhout¹*

Purpose: 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) using a 7 Tesla (T) MRI scanner in stand-by mode.

Methods: 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.

Results: 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 the performance on any of the tasks.

Conclusion: 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 study and, presumably, previous experiments. **Magn Reson Med 74:840-849, 2015.** © **2014 Wiley Periodicals, Inc.**

Key words: magnetic resonance imaging (MRI); static magnetic fields (SMF); static magnetic stray fields; low frequency movement induced time-varying magnetic fields (TVMF); cognition; exposure

INTRODUCTION

Magnetic resonance imaging (MRI) is a popular diagnostic and research instrument, with more than 20,000 systems presently in use worldwide (1). Since the introduction of the first scanner toward the end of the 1970s, advancing

© 2014 Wiley Periodicals, Inc.

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 (2,3). 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]) (4). 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) (5), although no changes in neurocognitive function were observed at these field strengths inside the scanner (6,7). 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 (8), attention/concentration, visuospatial orientation (9), and postural body control (10) were observed.

To unravel the origins of these neurocognitive effects, it is important to separate effects of different types of magnetic fields, because they point toward different mechanisms (11). It is still debated whether observed effects outside the bore are due to exposure to SMF alone or 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 (5,11,12). However, whether stimulation of the vestibular system by SMF can account for changed neurocognitive performance is still unclear (13). 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 (14). It is important to know which exposures affect neurocognitive functions, because this could have practical implications for employees and patients. In particular, employees such as radiographers, anesthesiologists, 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 (2), it is important to know which exposures should be controlled.

¹Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands.

²Helmholz Institute, Utrecht University, Utrecht, The Netherlands.

Grant sponsor: The Netherlands Organization for Health Research; Grant numbers: 85100001 and 85800001.

^{*}Correspondence to: Hans Kromhout, Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80178, 3508 TD Utrecht, The Netherlands. E-mail: h.kromhout@uu.nl

Additional Supporting Information may be found in the online version of this article.

Received 29 April 2014; revised 12 August 2014; accepted 14 August 2014 DOI 10.1002/mrm.25443

Published online 15 September 2014 in Wiley Online Library (wileyonlinelibrary.com).

A)							
Trair Ses	nings Session 1 30 min. Ses	ssion 2 Next Session 3 30 min. Session 4					
B)							
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					
	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					
v	Head movement or break RBMT recall	Recall the short story read by the test leader at the start of the session					

FIG. 1. A: Setup of the experiment. Each subject underwent a training session followed by four experimental sessions in a randomized crossover design. An exposure and corresponding sham exposure session were always conducted on the same day. B: An experimental session took an average of 15 min, including five different neurocognitive tasks as specified.

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 mechanisms 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).

METHODS

Subjects

A total of 36 healthy volunteers participated in the experiment (men, n = 6; women, n = 30) with an average age of $22 \pm SD 2.74$ y (range, 18–30 y) 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: preg-

nancy, 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 had undergone 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 (15)]. In line with our previous experiments (9), 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.

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 ($210 \times 140 \times 90$ 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 that revealed an effect of exposure to magnetic fields in at least one of the previous experiments (8,9,16,17) 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 Behavioral Memory Test (RBMT) to assess (long-term) verbal memory (18), the line-bisection task to test visuospatial orientation (19), the pursuit aiming task to test eye-hand coordination (20), 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 (21).

Data Analysis

N

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 for 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:

farginal mean =Intercept + R.C._{exposure condition}
+ 0.25 *
$$\left(\sum R.C._{Session1-4}\right)$$

+ (0.17 * R.C._{male} + 0.83 * R.C._{female})
+ $\left(0.28 * R.C._{not motion sick}\right)$
+ 0.61 * R.C._{moderate motion sick}
+ 0.11 * R.C._{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 (22).

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 ⁹ (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

Table 1

Average Test Performance, Standard Deviations (SD) and Geometric Means (GM) for Each Neurocognitive Test in the Sham Condition, SMF Condition, Sham Condition with Additional Head Movements (sham + HM), and SMF Condition with TVMF Induced by Head Movements (SMF + TVMF) (N=36)

		Sham		SMF			S	Sham + HM			SMF + TVMF	
Task and measures	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												
Small												
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
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
Reaction time ^e												
Simple												
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												
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												
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 values are presented as raw untransformed data.

^aRecall of a short story read by the test leader, given in correct words and the difference in %.

^bMark the middle of 20 horizontal lines; the center of the line is defined as 100.0 %.

^cPlace dots in small circles in 60 s. Speed = total marked items, precision = % correct items of total marked items.

^dRecognizing the direction of lines with shrinking contrast and different cycle frequencies, for different cycles per degree (cpd).

^ePress the target button when it lights up and return to the home button in ms. Simple: one button option. Complex: nine button options. Inhibition: press button left of the button that lights up. Reaction time = time to release home button after target button lights up. Motion time = time needed to go from home button to target button. Disengagement time = time needed to release the target button.

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 visuospatial 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

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)

· · · ·	· · · · · · · · · · · · · · · · · · ·	Estimated	Standard	95% Confidence	
Task and measures		marginal mean	error	interval	P^{a}
BBMT					
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	01011
	Sham + HM	11.06	0.56	9 93 12 18	0 079
		11.00	0.50	5.56, 12.16	0.075
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
b					
Line Bisection ^b	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
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.1.					
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
		105 51	1.05	070 00 110 00	
3.0 cpd	Snam	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 and	Cham	200.00	1.07	060 01 050 06	
5.0 cpu	SHALL	308.32	1.07	200.01, 303.90	0.045
	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
12.0 000	Sham	106.01	1 10	Q/ 00 10/ 70	
12.0 cpu	SHAIII	100.91	1.12	04.93, 134.70	0.004
	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

(Continued)

TABLE 2. Continued

		Estimated	Standard	95% Confidence	
Task and measures		marginal mean	error	interval	P^{a}
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
Reaction time (in ms) Simple					
Reaction time	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
Motion time	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
Disengagement	Sham	132.41	5.11	122.12, 142.70	
time	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					
Reaction time	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
Motion time	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
Disengagement	Sham	131.67	5.00	121.58, 141.76	
time	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					
Reaction time	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
Motion time	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
Disengagement	Sham	129.89	4.56	120.71, 139.07	
time	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

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

^aPairwise comparison between sham versus SMF and sham + HM versus SMF + TVMF, bold values; statistical significant at p < 0.05. ^bModel was adjusted for hand preference.

^ccpd, cycles per degree.

the left is normally found among healthy subjects (23). 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.



FIG. 2. Estimated test performance on the RBMT with corresponding standard errors based on a mixed model analysis in the sham condition, SMF condition, sham condition with additional head movements (sham + HM), and SMF condition with additional TVMF induced by head movements (SMF + TVMF) in the current study (N = 36) and in the previous experiment (N = 30). *P < 0.05.

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, visuospatial orientation and eyehand coordination 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 (24,25). Therefore, our current and previous findings (9) point predominantly toward specific aspects of attention,

A) Reaction time



FIG. 3. Estimated test performance on a 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, SMF condition, sham condition with additional head movements (sham + HM), and SMF condition with additional TVMF induced by head movements (SMF + TVMF) in the current study (N = 36) and in the previous experiment (N = 30). **P* < 0.05; ***P* < 0.001.



FIG. 4. Estimated test performance on the line bisection task with corresponding standard errors based on a mixed model analysis in the sham condition, SMF condition, sham condition with additional head movements (sham + HM), and SMF condition with additional TVMF induced by head movements (SMF + TVMF) in the current study (N = 36) and in the previous experiment (N = 30). *P < 0.05.

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 (9), 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 (5,12). 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. (26) for a review]. Exposure to TVMF can result in electromagnetic induction, which can inhibit or facilitate neuron communication directly (14,27). 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 (28)]. 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 (29), 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 (Sup. Table S1). This could have resulted in larger between-subject



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



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

variability in test performance as shown by the larger standard deviations (Sup. 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 wk 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) (Sup. 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 nonsignificant decreased attention and concentration are more likely attributable to simultaneous exposure to SMF and movement-induced TVMF rather than SMF alone.

ACKNOWLEDGMENTS

We thank Peter Luijten for providing the 7 T MRI room, Rosemarijn Hoekstra, Jorinde Timmer and all study participants for their contributions during the experiments.

REFERENCES

- 1. Moser E, Stahlberg F, Ladd ME, Trattnig S. 7-T MR—from research to clinical applications? NMR Biomed 2012;25:695–716.
- Schaap K, Christopher-De Vries Y, Slottje P, Kromhout H. Inventory of MRI applications and workers exposed to MRI-related electromagnetic fields in the Netherlands. Eur J Radiol 2013;82:2279–2285.
- Edelstein WA, Hutchison JM, Smith FW, Mallard J, Johnson G, Redpath TW. Human whole-body NMR tomographic imaging: normal sections. Br J Radiol 1981;54:149–151.
- 4. Schaap K, Christopher-de Vries Y, Mason CK, de Vocht F, Portengen L, Kromhout H. Occupational exposure of healthcare and research staff to static magnetic stray fields from 1.5–7 Tesla MRI scanners is associated with reporting of transient symptoms. Occup Environ Med 2014;71:423–429.
- Roberts DC, Marcelli V, Gillen JS, Carey JP, Della Santina CC, Zee DS. MRI magnetic field stimulates rotational sensors of the brain. Curr Biol 2011;21:1635–1640.
- Heinrich A, Szostek A, Meyer P, et al. Cognition and sensation in very high static magnetic fields: a randomized case-crossover study with different field strengths. Radiology 2013;266:236–245.
- Lepsien J, Muller K, von Cramon DY, Moller HE. Investigation of higher-order cognitive functions during exposure to a high static magnetic field. J Magn Reson Imaging 2012;36:835–840.
- de Vocht F, Stevens T, van Wendel-de-Joode B, Engels H, Kromhout H. Acute neurobehavioral effects of exposure to static magnetic fields: analyses of exposure-response relations. J.Magn Reson Imaging 2006; 23:291–297.
- van Nierop LE, Slottje P, van Zandvoort MJ, de Vocht F, Kromhout H. Effects of magnetic stray fields from a 7 Tesla MRI scanner on neurocognition: a double-blind randomised crossover study. Occup Environ Med 2012;69:759–766.
- van Nierop LE, Slottje P, Kingma H, Kromhout H. MRI-related static magnetic stray fields and postural body sway: a double-blind randomized crossover study. Magn Reson Med 2013;70:232–240.
- Glover PM, Cavin I, Qian W, Bowtell R, Gowland PA. Magnetic-fieldinduced vertigo: a theoretical and experimental investigation. Bioelectromagnetics 2007;28:349–361.
- Antunes A, Glover PM, Li Y, Mian OS, Day BL. Magnetic field effects on the vestibular system: calculation of the pressure on the cupula due to ionic current-induced Lorentz force. Phys Med Biol 2012;57: 4477–4487.
- Hanes DA, McCollum G. Cognitive-vestibular interactions: a review of patient difficulties and possible mechanisms. J Vestib Res 2006;16: 75–91.
- Iles JF. Simple models of stimulation of neurones in the brain by electric fields. Prog Biophys Mol Biol 2005;87:17–31.
- Fuentes MA, Trakic A, Wilson SJ, Crozier S. Analysis and measurements of magnetic field exposures for healthcare workers in selected MR environments. IEEE Trans Biomed Eng 2008;55:1355–1364.
- 16. de Vocht F, Glover P, Engels H, Kromhout H. Pooled analyses of effects on visual and visuomotor performance from exposure to magnetic stray fields from MRI scanners: application of the Bayesian framework. J Magn Reson Imaging 2007;26:1255–1260.
- 17. de Vocht F, van-Wendel-de-Joode B, Engels H, Kromhout H. Neurobehavioral effects among subjects exposed to high static and gradient magnetic fields from a 1.5 Tesla magnetic resonance imaging system a case-crossover pilot study. Magn Reson Med 2003;50:670–674.
- Wilson B, Cockburn J, Baddeley A, Hiorns R. The development and validation of a test battery for detecting and monitoring everyday memory problems. J Clin Exp Neuropsychol 1989;11:855–870.
- Schenkenberg T, Bradford DC, Ajax ET. Line bisection and unilateral visual neglect in patients with neurologic impairment. Neurology 1980;30:509–517.
- 20. World Health Organization. Operational guide for the WHO neurobehavioural core test battery. Geneva, Switzerland: World Health Organization; 1986.

- van Zomeren AH, Brouwer WH. Head injury and concepts of attention. In: Levin HS, Grafman J, Eisenberg HM, editors. Neurobehavioral recovery from head injury. New York: Oxford University Press; 1987. p 398–415.
- 22. Gilmore GC. Scoring of contrast sensitivity on Vistech charts. J Neurol Sci 2002;205:85; author reply 87.
- 23. Bradshaw JL, Nettleton NC, Nathan G, et al. Bisecting rods and lines: effects of horizontal and vertical posture on left-side underestimation by normal subjects. Neuropsychologia 1985;23:421–425.
- 24. Ganor-Stern D, Seamon JG, Carrasco M. The role of attention and study time in explicit and implicit memory for unfamiliar visual stimuli. Mem Cognit 1998;26:1187–1195.
- 25. Lezak DHaM. Separating memory from other cognitive problems. In: Baddeley AD, Kopelman MD, Wilson, BA, editors. Handbook of memory disorders. Chichester, England: John Wiley & Sons; 2002. p 637–655.
- 26. Utz KS, Dimova V, Oppenlander K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. Neuropsychologia 2010;48:2789–2810.
- Silva S, Basser PJ, Miranda PC. Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus. Clin Neurophysiol 2008; 119:2405-2413.
- 28. Reason JT, Brand JJ. Motion sickness. London: Academic Press; 1975.
- 29. International Commission on Non-Ionizing Radiation Protection. Guidelines for limiting exposure to electric fields induced by movement of the human body in a static magnetic field and by time-varying magnetic fields below 1 Hz. Health Phys 2014;106: 418-425.