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Experimental human study concerning possible effect of 50 Hz magnetic fields on sleep and markers of Alzheimer's disease – Study design and exposure facility

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Abstract

In order to investigate possible effects of 50 Hz magnetic fields on sleep and markers of Alzheimer's disease (AD), an experimental human study is presently carried out at the Competence Center of Sleep Medicine at Charité Universitätsmedizin Berlin. In total, 40 adults (20 females, 20 males; age: 55-75 years) will be included in a double-blind, randomized, sham-controlled cross-over study. A screening and adaptation night will be followed by three experimental study nights (each separated by a 1-week interval) in which participants are exposed for eight hours to three exposure conditions (low, high, sham). Possible effects of exposure on objective sleep (measured by polysomnography), on self-rated sleep quality (measured by questionnaires), as well as on memory consolidation and biomarkers of AD will be evaluated.

Whole body magnetic field exposure of the sleeping subjects is accomplished by a custom-tailored exposure system optimally fitted to the experimental sleeping room. The exposure system allows for exposure levels of up to 30 µT, with maximum homogeneity deviation of ± 20 %, the latter being achieved by a special system design due to the particular conditions in the experimental sleeping room. Sham condition is realized by antiparallel currents in the coils. A corresponding control software enables double-blind application of the specified experimental conditions and recording of all relevant exposure metrics for quality assurance.

1 Introduction

At the Competence Center of Sleep Medicine of Charité Universitätsmedizin Berlin, a provocation study is being conducted on the question of possible influences of extremely low frequency magnetic fields (ELF-MF) on sleep and markers of Alzheimer's disease. This paper summarizes the study design and the technical aspects of the exposure facility, particularly developed for this study.

2 Methods

2.1 Study design

In total, 40 participants (20 females, 20 males) within the age range of 55 to 75 years take part in a double-blind, randomized, sham-controlled cross-over study. Only women already in their menopause are included. Participants must be right-handed, non-smokers, and must not suffer from any sleep-disorder according to the International Classification of Sleep Disorders (ICSD-3) of the American Academy of Sleep Medicine (AASM) [1]. Diseases typical of age (e.g., high blood pressure) are accepted as long as they do not interfere with sleep and cognition. Extreme morning and evening types and people who take psychotropic drugs or drugs that affect sleep are excluded. After a stepwise comprehensive screening process, including a medical examination and a screening night in the sleep laboratory, study participants undergo three experimental nights in the sleep laboratory (separated by one week each). Sleep is recorded according to the standard criteria of the AASM [2], analyzed by a computer-assisted scoring system according to the AASM and controlled by independent experts [3].

Whether extremely low frequency magnetic fields have an impact on sleep-dependent memory consolidation processes is evaluated by a declarative and a procedural memory task, which participants will complete in the evening and in the morning of the experimental nights. In addition, biomarkers of AD (amyloid beta, tau protein) and melatonin are analyzed from blood and urinary samples during experimental nights.

To control for a regular sleep-wake rhythm and sufficient sleep prior to the experimental nights, all participants wear an actigraph for the time when participating in the study.

The study protocol was approved by the ethics committee of the Charité - Universitätsmedizin Berlin. Written informed consent is given by all participants and they are paid for their participation.

2.2 Exposure facility

The key requirements for the exposure can be summarized as follows:

- Uniform exposure of the entire body of sleeping subjects (volume of interest 200 x 80 x 30 cm^3 above the top of the mattress) to selectable magnetic flux densities of up to 30 µT at 50 Hz
- Maximum field inhomogeneity ± 20 %
- Magnetic field generation by three independent pairs of coils, with main field directions along the longitudinal

axis of the body, normal to the frontal plane of the body and normal to the sagittal plane of the body

- Field vector direction flexibly controllable by software
- Coil arrangement, so that the subject can leave the bed unassisted and unrestricted (no "cage formation" by the coils for escape in case of emergency)
- Establishment of a sham exposure condition (SHAM) by opposing currents in the coil windings, with the same current as during exposure (VERUM)
- Only the coil assembly located inside the sleeping room; all other components of the system (signal generator, amplifier, control computer) should be located outside of the sleeping room to avoid disturbing noise
- Vibration-damped design and placement of field-generating coils
- Software-controlled, randomized, and double-blind application of three different, freely selectable exposure levels (LOW / HIGH / SHAM); determination of LOW and HIGH (max. 30 µT) according to study protocol
- Monitoring and encrypted recording of the exposure-relevant system parameters (magnetic flux density, coil currents, audio noise, vibration) during the experiments

A schematic overview of the system concept is depicted in Figure 1. The confined space in the sleeping room in combination with some of the key data described above require a custom-tailored design of the coils (Figure 2).
To ensure the homogeneity demands in vertical direction, the bed must be placed on a pedestal so that the top edge of the mattress is approximately 100 cm above the floor of the sleeping room. Another challenge for the system development is the radio frequency shielding (aluminum sheets) incorporated in the floor, ceiling, and walls of the sleeping room in combination with small remaining distances between the coils and the walls and the floor, respectively. This leads to noticeable losses and an increase in coil impedance. Particularly, the lower z-coil close to the floor must be lifted about 18 cm above floor level to reduce this effect to a level at which the output impedance requirements of the amplifier are sufficiently met. In addition, there is significant field distortion observable, especially with field vector orientation in the x-direction, because the distance of the x-coil next to the service corridor (Figure 2) to the nearest wall is approximately 15 cm while it is approximately 1 m for the opposite x-coil. The field homogeneity requirements are met by driving the two x-coils separately with different current strengths.
Since there is no information yet in which spatial orientation of the generated magnetic field the strongest potentially existing biological effect is to be expected, an automatic software-controlled systematic variation of the orientation of the resulting magnetic field vector (at constant vector magnitude) is implemented to achieve a uniform distribution of magnetic field vector alignment throughout the exposure period, while ensuring that no abrupt changes occur (could lead to artifacts in the EEG recording that could compromise blinding). Additionally, special care is taken to ensure an equal distribution of magnetic field vector alignment during the different sleep phases. Therefore, corresponding time functions for weighting factors of the coil currents for the three main field directions x, y, and z are developed and implemented in the control software. The functions are based on 1800 spatial directions uniformly distributed over an imaginary spherical surface (900 pairs with opposite sense of direction). With a pseudo-random sequence, all space directions are set one after the other, whereby the transition takes place in 2 seconds each with constant angular velocity. A few minutes of the course, corresponding to individual sleep phases, already cover correspondingly different directions of the magnetic field vector, so that there is a uniform exposure with respect to the vector orientation.

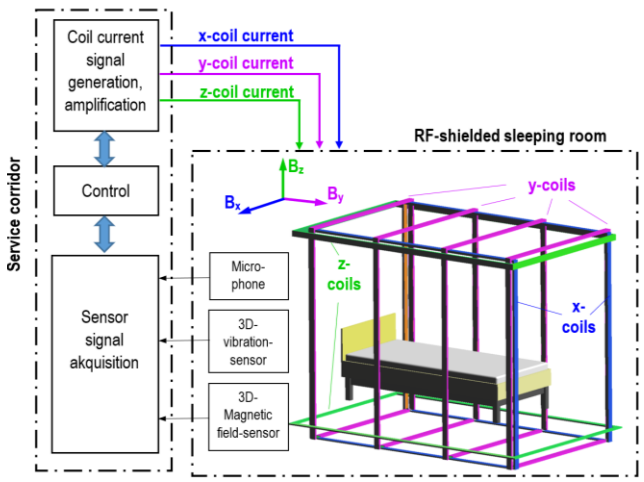

Figure 1. Concept of the exposure system.

The control software for the double-blind sequence control of the experiments and for recording of the exposure-relevant data is programmed in LabView^{TM}. The graphical user interface is designed in a simple and clear way and secured against operating errors. For quality assurance purposes, all coil currents, the magnetic flux density measured below the bed (by means of a custom-made 3D coil magnetic field sensor), vibrations of the bed (by means of a 3D accelerometer ASC 5411LN mounted on the back side of the bed headboard), and the sound level in dBA as well as the time function of the microphone signal (by means of the sound meter Sefram 9836, mounted on the back side of the bed headboard) are measured continuously and recorded in encrypted form by the control software at regular intervals of approximately 5 s.

2.3 Dosimetric characterization

The resulting field distribution in the volume of interest (200 x 80 x 30 cm^3) above the top of the mattress is measured separately for x-, y-, and z-coils.
The induced electric field strength (E_i) inside the body tissues of the three different anatomical body models Duke (34-year-old male), Ella (26-year-old female), and Louis (14-year-old boy) [4] for a frequency of 50 Hz are computed using the magneto-quasi-static solver of the

Sim4Life simulation platform (ZMT Zurich MedTech AG, Zurich, Switzerland [5]). Dielectric tissue properties are basically chosen based on the IT'IS tissue database [6], only the skin conductivity is defined as 0.2 S/m according to more recent scientific findings [7]. All computations are carried out with a computational grid of 1 x 1 x 1 mm^3.

In addition to that, brain region-specific evaluations are also performed for the Duke body model, based on the Talairach Atlas [8], using the corresponding evaluation tool of the SEMCAD X simulation platform (data not shown).

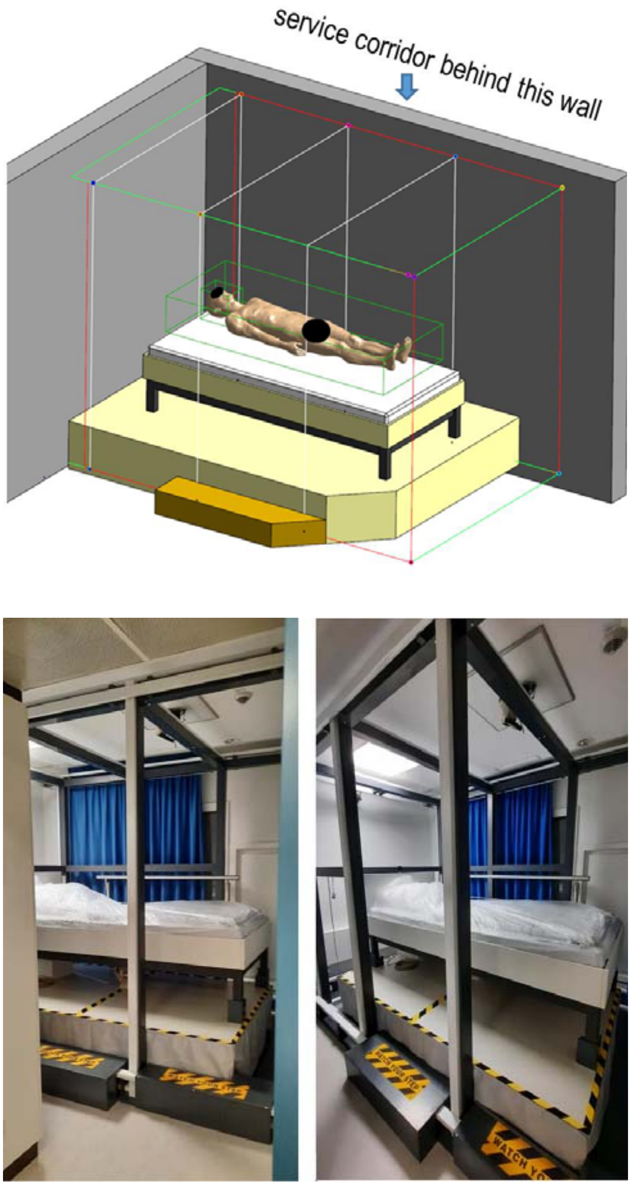

Figure 2. Arrangement of the coils in the sleeping room. Top: CAD model with coil current paths and anatomical body model. Bottom: photographs of the coils after installation in the sleeping room.

3 Results

Figure 3 depicts the remaining field inhomogeneity of less than ± 20%.
Table 1 summarizes the properties of the developed exposure system including the computational results of the induced electric field strengths inside CNS and PNS tissues in terms of the maximum (p100), the 99.9th percentile (p99.9), and the 99th percentile (p99.0) of the 2 x 2 x 2 mm^3 volume averaged E_i ($E_{i,avg}$).

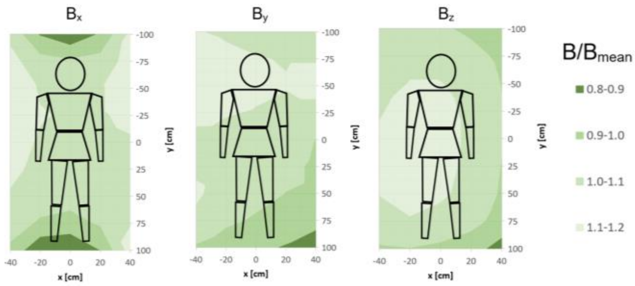

Figure 3. Magnetic field distribution on top of the mattress, shown separately for the field vector oriented in x-, y-, and z-direction. Shown data is normalized to the mean over the reference volume of 200 x 80 x 30 cm^3 above the mattress.

Table 1. Summary of the dosimetric calculations (50 Hz)

		$E_{i,avg,CNS}$ [V/m/T]			$E_{i,avg,PNS}$ [V/m/T]		
		Bx	By	Bz	Bx	By	Bz
Duke	p100	43.2	27.7	30.7	236	124	220
	p99.9	22.1	18.7	20.2	52.2	46.2	87.6
	p99.0	17	15.4	16.4	31.9	27.6	50
Ella	p100	29.3	27.8	31.3	151	96.1	273
	p99.9	18.7	18.1	18.7	47.6	38.1	78.1
	p99.0	15	14.6	15	28.5	23.2	48.5
Louis	p100	31.2	26.3	30.6	298	96.9	145
	p99.9	18	18.4	19.5	42.2	39.9	71.1
	p99.0	14.9	15.2	16	25.6	24.2	42.2

It is noted that tissue conductivities, especially in the low frequency range, are still subject to considerable uncertainties. The database mentioned above provides conductivity values from parameter models for the frequency range 10 Hz – 100 GHz, as well as statistical data from the literature of measurements explicitly performed in the low frequency range (IT'IS LF Conductivity Database). A comparison of these different data sources for a frequency of 50 Hz shows significant differences for the conductivities of individual tissues (up to a factor of approx. 6). Therefore, all simulations corresponding to this project are performed three times, each using the following data sources: IT'IS LF Conductivity Database V 4.0, IT'IS LF Conductivity Database V 4.1, IT'IS Parametric Dielectric Properties Database V 4.1 [6]. The values for $E_{i,avg,CNS}$ and $E_{i,avg,PNS}$ given in Table 1 correspond to mean values of the results, calculated using the above three data sources. The scatter range (MAX, MIN) of the results is up to approx. 50 % for CNS tissue and 70 % for PNS tissue.

4 Discussion & Conclusion

A custom-tailored 50 Hz magnetic field exposure system for homogeneous whole-body exposure of human subjects during sleep is developed and dosimetrically characterized. The exposure system enables exposure levels of up to 30 µT. SHAM condition is realized by antiparallel currents in the coils. A corresponding control and recording software allows double-blind application of the specified experimental conditions, and all relevant exposure metrics are continuously monitored and recorded in 5 s intervals for quality assurance. The developed exposure system is presently used in an ongoing study at the Competence Center of Sleep Medicine of Charité Universitätsmedizin Berlin concerning the question of possible influences of extremely low frequency magnetic fields (ELF-MF) on sleep and markers of Alzheimer's disease.

Acknowledgements

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