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A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation ☆

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Abstract

Objective: The *H*-coils are a new development in transcranial magnetic stimulation (TMS) research, allowing direct stimulation of deeper neuronal pathways than does standard TMS. This study assessed possible health risks, and some cognitive and emotional effects, of two *H*-coil versions designed to stimulate deep portions of the prefrontal cortex, using several stimulation frequencies.
Methods: Healthy volunteers ($n = 32$) were randomly assigned to one of four groups: each of two *H*-coil designs (*H*1/*H*2), standard figure-8 coil, and sham-coil control. Subjects were tested in a pre–post design, during three increasing (single pulses, 10 Hz, and 20 Hz) stimulation sessions, as well as 24–36 h after the last stimulation.
Results: The major finding of the present study is that stimulation with the novel *H*-coils was well tolerated, with no adverse physical or neurological outcomes. Computerized cognitive tests found no deterioration in cognitive functions, except for a transient short-term effect of the *H*1-coil on spatial recognition memory on the first day of rTMS (but not in the following treatment days). On the other hand, spatial working memory was transiently improved by the *H*2-coil treatment. Finally, the questionnaires showed no significant emotional or mood alterations, except for reports on 'detachment' experienced by subjects treated with the *H*1-coil.
Conclusions: This study provides additional evidence for the feasibility and safety of the two *H*-coil designs (*H*1/*H*2).
Significance: The *H*-coils offer a safe new tool with potential for both research and clinical applications for psychiatric and neurological disorders associated with dysfunctions of deep brain regions.

Keywords: Deep transcranial magnetic stimulation; rTMS; *H*-coil; Safety; Cognitive; Mood

1. Introduction

Current transcranial magnetic stimulation techniques enable only superficial stimulation of the brain, as the intensity of the electric field decreases rapidly as a function of tissue depth. Stimulating deeper brain regions requires a high intensity that cannot be achieved by currently available stimulators. Moreover, even special designs of stimulators with greater power outputs would not allow safe stimulation of much deeper brain sites, as the intensity required, using standard TMS coils (such as the figure-8 coil), could lead to undesirable side-effects induced in the more superficial regions (Nadeem et al., 2003).

These limitations have led to the development of the *H*-coil, a new TMS coil that has been designed to allow deeper brain stimulation without a significant increase of fields induced in superficial cortical regions. Mathematical models in conjunction with tests performed in a phantom brain model demonstrated the ability of the *H*-coil to stimulate deep brain regions (Roth et al., 2002). A study performed

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on healthy volunteers confirmed that the rate of intensity decay as a function of distance is much slower when using the *H*-coil as compared to the standard figure-eight coil (Zangen et al., 2005). Using the parameters of the current study, the *H*-coil induces an effective field at depth of about 3 cm below the skull, compared to less than 1 cm for the figure-8 coil (Roth et al., 2007).

Numerous studies have tested the effect of rTMS on major depression using standard TMS coils. Yet results have been especially poor in treating elderly patients (Frazer et al., 2005). It has been suggested that the observed inefficacy may be a result of the progressive shrinking of brain tissue observed with age, which would therefore result in an increased coil to prefrontal cortex distance. Deep rTMS may prove to be beneficial in treating depression in older patients who have increased distance from the skull to the prefrontal cortex (more than 1.7 cm) (Kozel et al., 2000).

The ability of the *H*-coil to directly stimulate deeper brain regions (e.g., ventral prefrontal cortex and its connections to the nucleus accumbens and ventral tegmentum) that are associated with reward and motivation functions may be beneficial in the treatment of depression, addiction (Robinson and Berridge, 2003), and negative symptoms in schizophrenia (Kelley et al., 2002; Juckel et al., 2006). In addition to the potential clinical benefits of the *H*-coils in various psychopathological and neurological conditions, the ability to induce direct stimulation in deeper brain sites opens a window to many basic research questions (Zangen et al., 2005; Roth et al., 2007).

The aim of the current study was to evaluate safety aspects of deep TMS using the *H*-coil at frequencies up to 20 Hz. In addition, transient cognitive and emotional outcomes of deep TMS were compared to those of standard or sham TMS. Two versions of the *H*-coil were used: (1) The *H*1-coil, which produces the most effective field in the anterior-posterior direction, and preferentially induces stimulation in the left prefrontal cortex; (2) the *H*2-coil, which produces the most effective field in the right-left direction (lateral-medial axis) and equally affects both hemispheres (Roth et al., 2007).

Healthy volunteers were divided into four groups in order to compare the effects of these two *H*-coil versions to those of a standard commercial *figure-8* coil, and a sham-*H*-coil (see Table 1 for study design). Safety measures and appropriate tests were chosen according to the safety guidelines for TMS studies (Wassermann, 1996) and our previous study using the *H*-coil (Zangen et al., 2005). All subjects were given an extensive physical and neurological examination, immediately before and after each TMS stimulation session, as well as 24–36 h after the last TMS session. In order to identify dose-dependent effects and minimize adverse events, the current study employed progressively increasing TMS frequencies (Wassermann et al., 1996).

In addition, this study examined transient cognitive effects of the *H*-coil as compared to standard TMS. Transient effects may be short-term, lasting seconds or minutes, or longer-term, as measured in this study up to several days. In previous studies, low frequency standard TMS was used to study the neural basis underlining cognitive functions (Anand and Hotson, 2002; Rossi and Rossini, 2004). These extensive studies indicated that TMS is able to interfere with higher brain functions, such as language, working memory, sensory-motor processing and attention. For example, standard TMS has been instrumental in demonstrating involvement of the dorsolateral prefrontal cortex in working memory and long-term episodic memory (Grafman and Wassermann, 1999; Rossi and Rossini, 2004) and confirmed the importance of parietal and frontal cortex in attention (e.g., Jahanshahi et al., 1997; Hilgetag et al., 2001). Furthermore, standard TMS not only interferes with cognitive functioning, but, in some studies, has been shown to facilitate various aspects of cognitive performance such as verbal memory (Jahanshahi et al., 1997). Standard TMS over the PFC can also facilitate faster and more accurate retrieval of semantic memory (Grafman and Wassermann, 1999). In contrast, right DLPFC rTMS transiently (short-term) increased response times for invalid trials in a cued reaction time task (Rounis et al., 2006). Because the underlying mechanisms for these effects are not yet fully understood, and these effects are not easily predictable, the prospect of using TMS as a possible therapeutic tool for cognitive impairments represents an intriguing challenge (Rossi and Rossini, 2004).

Additionally, we hypothesized that the different versions of the *H*-coils induce activation of different circuits, which would lead to differential effects on cognitive functions. For this aim we used well-validated computerized neuropsychological tests, associated with temporal, parietal and frontal lobe functions.

Finally, this study examined transient emotional effects of the *H*-coils compared to standard TMS, using clinical assessment interviews and subjective report forms. Standard TMS has been reported to affect emotions in a lateralized fashion, with left prefrontal cortex stimulation inducing increased self-rating of sadness and decreased self-rating of happiness, while right prefrontal cortex stimulation inducing decreased self-rating of sadness (George et al., 1996; Pascual-Leone et al., 1996). Furthermore, several studies report clinical improvement in severely depressed subjects after daily standard TMS over the left prefrontal cortex using high frequencies, while other studies indicate that low-frequency TMS over the right prefrontal has antidepressant properties (Burt et al., 2002), and one study used both (Fitzgerald et al., 2006). Therefore, the present study compared transient emotional effects induced by the *H*-coils, the figure-eight coil and a sham coil, using different stimulation frequencies.

2. Materials and methods

2.1. Subjects

Thirty-nine healthy volunteers were recruited using newspaper advertisements, and were assessed for the study,

Table 1
General overview of the study design'

Treatment group	Single pulses (day 1 visit)			10 Hz (day 3 visit)			20 Hz (day 5 visit)		
	Pre-TMS evaluation	**TMS stimulation**	**Post-TMS evaluation**	**Pre-TMS evaluation**	**TMS stimulation**	**Post-TMS evaluation**	**Pre-TMS evaluation**	**TMS stimulation**	**Post-TMS evaluation**
H1-coil stimulation	Audiogram Physical Neurological Cognitive Emotional	TMS Treatment	Physical (+ VAS & Scalp inspection) Neurological Cognitive Emotional	Physical Neurological Cognitive Emotional	TMS Treatment	Physical (+ VAS & Scalp inspection) Neurological Cognitive Emotional	Physical Neurological Cognitive Emotional	TMS Treatment	Audiogram Physical (+ VAS & Scalp inspection) Neurological Cognitive Emotional
H2-coil stimulation									
Figure-8 coil stimulation									
Sham coil stimulation									

Notes: Subjects of all 4 treatment groups (*H*1-coil, *H*2-coil, figure-8 coil and sham coil) followed an identical experimental design (except for type of TMS stimulation).

which was done in the Shalvata Mental-Health Center, Israel. Initial screening was conducted using a medical interview and a safety-screening questionnaire for TMS. Of the 39 volunteers, 35 healthy right-handed males and females, aged 18–50 years, non-hospitalized, with no evidence of psychiatric, neurological or physical disorder, fulfilled the inclusion criteria (as evaluated by standard physical and neurological examinations); two did not meet the inclusion criteria, and two refused to participate.

All of the subjects were naïve to TMS; they all came in for treatment at separate times so as not to encounter other subjects; all were interviewed to ensure they did not come to the study by hearing about it from a friend who already served as a subject. The purpose was to exclude subjects who might have prior expectations as to the effects of TMS, which might influence their responses and reports.

Exclusion criteria included any current medical, surgical or psychiatric illness, history of psychiatric or neurological illnesses (including brain injury), history of current hypertension, history of seizure or heat convulsion, history of epilepsy or seizure in first degree relatives, history of head injury, history of any metal in the head (outside the mouth), known history of any metallic particles in the eye, implanted cardiac pacemaker or any intracardiac lines, implanted neurostimulators, surgical clips or any medical pumps, history of frequent or severe headaches, history of migraine, history of hearing loss, known history of cochlear implants, history of drug abuse or alcoholism, pregnancy or not using a reliable method of birth control, systemic and metabolic disorders, inadequate communication skills or under custodial care. Candidates filling both inclusion and exclusion criteria were given a complete description of the study and signed written informed consents, according to the local and national Institutional Review Board (IRB) committee.

Subjects were randomly assigned (by receiving a sequential number from a computer-generated random list) to the following treatment groups: *H*1-coil TMS ($n = 9$), *H*2-coil TMS ($n = 9$), standard figure-8 TMS ($n = 8$) and sham-coil TMS ($n = 9$). Statistical analyses were conducted in order to ascertain that the *treatment* groups' (*H*1, *H*2, figure-8 and sham) subjects did not differ with regard to demographic variables.

Age and educational years were analyzed using a separate One-way Analysis of Variance (ANOVA) for each variable, using a between-subjects factor of *treatment*. The ANOVAs for age and educational years showed no differences between the four treatment groups (*H*1, *H*2, figure-8 and sham) [$F(3,28) = 1.218$, n.s., for age; $F(3,28) = 0.892$, n.s., for educational years]. A chi-square non-parametric test was used to analyze the distribution of gender across the research groups. The four treatment groups also did not differ in gender ($p = 0.612$). (See Table 2 for demographic data for final experimental subjects.)

2.2. Materials

2.2.1. TMS coils

Four TMS coils were used in the study (see Table 1 for study design), at a power level of 110% of motor threshold. It should be noted that the ability of the *H*-coils to activate deeper brain regions comes at the cost of focality (Zangen et al., 2005; Roth et al., 2007). Using the stimulation parameters of this study (i.e. 110% of the motor threshold),

Table 2
Demographic data

Treatment group	*H*1-coil ($N = 8$)	*H*2-coil ($N = 8$)	Figure-8 coil ($N = 8$)	Sham-coil ($N = 7$)	*p*
Age	26.75 (±1.94)	28.00 (±1.46)	23.75 (±0.62)	28.25 (±2.78)	n.s.
Education	14.88 (±0.93)	14.13 (±0.52)	13.38 (±0.53)	14.25 (±0.53)	n.s.
Gender (females/males)	4/4	5/3	4/4	3/5	n.s.

Demographic data; mean ± SEM of age (years), education (years) and gender (frequency) of subjects belonging to *H*1-coil, *H*2-coil, figure-8 coil and sham-coil treatment groups.
n.s., not significant.

the *H*1 and *H*2 coils can induce direct neuronal activation at depths of up to 3.5 cm within the lateral PFC, while the *figure-8* coil can induce direct activation at depths of up to 1.0 cm, at the dorsolateral PFC (Roth et al., 2007).

A. *H*1-coil: The *H*1-coil is an extracorporeal device positioned on the patient's scalp, designed to stimulate deep prefrontal brain regions, preferentially in the left hemisphere [for theoretical considerations and design principles, see (Roth et al., 2002, 2007; Zangen et al., 2005)]. The effective part of the coil, which has contact with the patient's scalp, includes 14 strips of 7–12 cm length (see Fig. 1a). These strips are oriented in an anterior-posterior axis. The frame of the inner rim of the coil is flexible in order to fit the variability in human skull shape.
B. *H*2-coil: The *H*2-coil is designed to stimulate deep prefrontal brain regions bilaterally (without any preference for either hemisphere). The effective part of the coil, which has contact with the patient's scalp, includes 10 strips of 14–22 cm length (see Fig. 1b). These strips are oriented in a right-left direction (lateral-medial axis). The frame of the inner rim of the coil is flexible in order to fit the variability in human skull shape.
C. *Figure-8 coil*: Standard commercial Magstim figure-8 coil with internal loop diameter of 7 cm (identical to that used in (Zangen et al., 2005)).
D. *Sham-coil TMS*: Sham TMS was delivered using the *H*2-coil, by connecting it to a switch which alternated it between real and sham TMS modes. The *H*2-coil was wound from double 14 AWG copper wire. In the sham mode, the electric current was delivered in opposite directions in each of the double wires. Hence, the induced electric field in the sham mode was negligible, while reproducing the auditory and visual sensations of real TMS mode.

2.3. Measures

2.3.1. Physical evaluation

Subjects filled out a short medical symptom questionnaire, evaluating headache, visual disturbances, weakness, paresthesia, instability, vertigo, tinnitus, changes in hearing or other bodily sensations. The questionnaire was filled out in the presence of a qualified clinician, who also performed a physical and neurological examination. Next, blood pressure and heart rate were measured.

2.3.2. Neurological evaluation

The examination included several measures: (a) Time taken to walk a standard distance of 10 meter (m) at a normal pace. (b) Time taken to walk a standard distance of 10 m at a fast pace. (c) Time taken to tandem-walk (one foot in front of the other) a standard distance of 5 m forward. (d) Time taken to tandem-walk a standard distance of 5 m backward. (e) Assessment of balance by recording the number of miss-steps in the tandem-walk backward. (f) Two point discrimination at the tip of right and left index fingers.

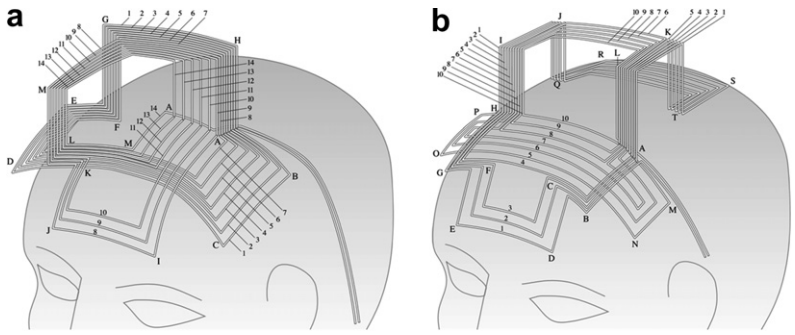

Fig. 1. Sketches of (a) the *H*1-coil and (b) the *H*2-coil, near a human head. The *H*1-coil orientation shown in the figure is designated for activation of structures in the prefrontal cortex, preferentially in the anterior-posterior direction of the left hemisphere. The *H*2-coil orientation shown in the figure is designated for activation of structures in the prefrontal cortex, preferentially in the lateral-medial direction without a significant side preference (Roth et al., 2007).

2.3.3. Emotional evaluation

Each subject was given a short clinical assessment; changes in orientation, mood, anger and irritability were recorded by a trained psychiatrist by means of an interview in which the subject was asked to report whether he experienced any kind of emotional, motor or visual change during or after the TMS session. In addition, subjects filled out the Positive and Negative Affect Schedule (PANAS) questionnaire. This is a 20-item self-report measure monitoring changes in the affective state of the subjects (Watson et al., 1988). The PANAS includes positive and negative affect factors (PA/NA), with subjects rating the extent to which they feel a particular emotion on a 5-point scale.

Two additional words were added at the end of the PANAS questionnaire. These two additional words were added to investigate possible dissociation feelings ('detached' and 'dizzy'), which some subjects had reported in a preliminary study. These added words, 'detached' and 'dizzy', have not been previously validated as part of the standard PANAS test.

2.3.4. Cognitive evaluation

Cognitive evaluation was conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB), which is sensitive to cognitive changes caused by a wide range of Central Nervous System disorders and medication side-effects (Robbins et al., 1994; Robbins et al., 1998). The CANTAB uses a computer with a *touch screen*, and affords a rapid and non-invasive assessment of cognitive function. Special care was given to choose tests that evaluated different cognitive domains, specific to different brain structures, allowing for more precise understanding of the effects of deep and standard TMS on brain functions.

Each subject was given five tests

1. *Reaction time* (*RTI*): Investigation of subject's reaction time is conducted in two steps: (1) (S*imple)* The stimulus appears on the touch screen in one location only and the subject's response latency for releasing the press pad in response to the onset of a stimulus (*simple reaction time*) is analyzed as a measure of processing (without a significant motor component). Then, time taken to touch the stimulus (on the touch screen) after the press pad has been released in trials where stimuli appear in one location only (*simple movement time*) is analyzed as a measure of the motor component. (2) (*Five-choice*) The same measures are analyzed, this time with the stimulus appearing in any one of five locations (*five-choice reaction time* and *five-choice movement time*). This task adds a decision element to the cognitive task. The RTI task gives elaborate information on the subject's visuo-motor skills (by acting as a single and multiple choice reaction time task). This motor task assesses the ability to acquire and perform a basic motor skill, as a training procedure in skills related to using the touch screen, and provides rough measures of speed and accuracy (index of the subject's motor skill).
2. *Spatial recognition memory* (*SRM*): Five identical squares are presented in series, each in a different location. One square is then presented at each target location, along with a square at a novel location. Subjects are asked to choose the square at the novel location they recognize from the initial, learning phase. This is a test of spatial recognition memory, used as an indicator of the ability of TMS to affect *medial temporal lobe* and *parietal lobe* functions (performance in the task was correlated with these functions, Stein, 1992; Milner et al., 1997).
3. *Pattern recognition memory* (*PRM*): Pairs of abstract visual stimuli are presented sequentially on the computer screen. Each stimulus is then presented alone and the subject is asked to choose the one that has been previously paired with it. The performance of this task is correlated with *medial temporal lobe* functions and is used as an indicator of the ability of TMS to affect temporal lobe associated cognitive functioning (Owen et al., 1995).
4. *Spatial memory span* (*SSP*): This is a computerized version of Corsi's block tapping test (Milner, 1971), which gives a measure of the subject's spatial memory span. The subjects are tested for their ability to remember the order in which a sequence of squares is highlighted on the screen (with the number of squares increasing progressively). Performance of this task is correlated with *ventrolateral prefrontal cortex* functions and together with the SWM task (see below) was used to assess the ability of TMS to affect frontal lobe associated cognitive functioning (Robbins et al., 1994).
5. *Spatial working memory* (*SWM*): A trial begins with a number of colored squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue 'counter' in each of the boxes. The subject must touch each box in turn until one opens with a blue 'counter' inside (a search). Returning to an empty box already sampled on this search is an error. The task assesses the ability of TMS to affect retention and manipulation of information in spatial working memory, and the ability to use a heuristic strategy (an executive function). Similar to the SSP task, this task is associated with *frontal lobe* functioning, and, in particular, brain areas such as the dorsolateral and ventrolateral frontal lobe, although the particular contributions of each region are still debated (Owen et al., 1996; Owen et al., 1999; Rowe and Passingham, 2001; Muller and Knight, 2006).

2.3.5. Headache intensity

Headache intensity was measured using Visual Analog Scales (VAS). The subjects were asked to rate their current headache intensity by marking X on a 1–10 (10 cm) visual scale. The subjects filled in the VAS questionnaire 5 min after the TMS session.

2.4. Interventions

2.4.1. TMS sessions

Subjects were instructed to insert earplugs to lessen any possible adverse effects on hearing. Next, the optimal spot on the scalp for stimulation of the right abductor pollicis brevis muscle was localized, and the individual motor threshold (MT) was determined by delivering single stimulations to the motor cortex. The exact threshold was determined by gradually increasing the intensity (using single pulse mode, applying one pulse every 5 s), and recording electrical activity in the abductor pollicis brevis using surface electrodes. Threshold was defined as the lowest intensity of stimulation able to produce motor evoked potentials of at least 50 μV in 5 of 10 trials. After defining the motor threshold, the coil was moved forward 5 cm anterior to the motor spot (over the left dorsolateral prefrontal cortex) and trains of either single pulses (day 1), 10 Hz (day 3) or 20 Hz (day 5) were delivered at 110% of the measured motor threshold. Each TMS session consisted of 42 trains. Each train was 1 s long and the inter-train interval was 20 s (George et al., 1999, 2000; Grunhaus et al., 2000; Gershon et al., 2003). Therefore, "single pulses" is one pulse every 20 s, repeated 42 times; "10 Hz" is 10 pulses given over 1 s, every 20 s, repeated 42 times; and "20 Hz" is 20 pulses given over 1 s, every 20 s, repeated 42 times.

2.4.2. Procedure

On the initial visit, subjects underwent an auditory threshold examination (audiogram) in a private auditory laboratory. These audiograms were later compared to audiograms performed 24 h after the last TMS session.

Each subject was randomly assigned to one of the four coils and did not change the coil throughout the whole study. Subjects participated in three TMS sessions differing in stimulation frequencies (single pulses, 10 Hz and 20 Hz).

Because this was the first test of the *H*-coils using high stimulation frequencies, all subjects received single pulses on the first day, 10 Hz two days later and 20 Hz after two more days. For research and comparison purposes it would have been more appropriate to use a random frequency order, but for safety reasons this was not done in the present study.

Every TMS visit included three stages: (1) *Pre-stimulation evaluations*, (2) *TMS session*, (3) *Post-stimulation evaluations*. A researcher blinded to the subjects' TMS coil treatment group conducted all evaluations.

During the entire study, the subjects were under the direct observation of a physician, and any adverse effects or subjective disturbance were immediately recorded and responded to. Subjects wishing to withdraw at any time were able to do so without prejudice.

2.4.3. Pre-stimulation and post-stimulation evaluations

Physical, neurological, emotional and cognitive evaluations were performed as described in *Measures* above, and were administered before and after each TMS session.

2.5. Data analysis

In the statistical discussions, the term "treatment" always refers to the different TMS coils used in the intervention: there were four *treatment* groups (*H*1, *H*2, figure-8 and sham). The term "frequency" always refers to the different days (and hence frequency) of the intervention: there were three *frequency* groups (day 1, Single Pulses; day 3, 10 Hz; day 5, 20 Hz). In all analyses, significant differences were followed by Scheffe post-hoc tests applied as *multiple comparison* procedures. Significant interactions were followed by Student *t*-tests or analysis of variance (ANOVA/ANVOVA/MANOVA) as indicated. In addition, as a correction for multiple comparisons, we required $p < 0.01$ for the five CANTAB tests and for the four emotional tests.

The ANOVAs were in a $4 \times 3 \times 2$ design, with a between-subjects factor of *treatment*, a within-subjects repeated factor of *frequency* and a within-subjects repeated measure of *pre–post* (pre-treatment performance compared to post-treatment performance).

3. Results

All data for the total of 31 subjects who completed the experimental procedure were statistically analyzed. From the original 35 subjects participating in the study, three dropped out of the study after the first TMS stimulation (single pulses stimulation) for non-research related reasons (logistics and scheduling of meetings). An additional subject's data were removed at the end as the subject was not cooperative with the evaluation tests.

Analysis of *short clinical assessment* protocols revealed that TMS in all groups was well tolerated by the subjects with no major side-effects. None of the following adverse outcomes occurred: accidental seizure induction, local pain of the scalp, transient headache and dizziness, transient hypotension, visual disturbances, weakness, paresthesia, instability, vertigo, tinnitus, or other bodily sensations. In addition, clinical inspection of the scalp area, conducted immediately after each stimulation session, showed no skin lesions.

3.1. Physical parameters

3.1.1. Auditory thresholds

In addition to the subjective descriptions of the subjects in the *short clinical assessment* (indicating no evidence for auditory changes), thresholds for air conduction were assessed separately for the left and right ear at frequencies of 0.25, 0.5, 1, 2, 4 and 8 kHz, comparing thresholds before the first TMS session and after the last stimulation.

No differential effects of the coils on the subjects' hearing thresholds (after sessions using single pulses, 10 Hz and 20 Hz) were detected, as well as no hearing loss in any subject (see Supplementary material, Statistics S1 and Figure S1).

3.1.2. Hemodynamic measures

Blood pressure was analyzed using separate three-way ANOVAs, for systolic and diastolic blood pressure. Heart rate was similarly analyzed. There was no evidence of hemodynamic abnormalities induced by any of the TMS coils (see Supplementary material, Statistics S2 and Table S1).

3.1.3. Neurological evaluation

Separate ANOVAs were conducted for the first four measures (a)–(d). Two measures were not included in the analyses (not shown): (e) number of missteps in the backward tandem-walk (which showed small variance, with most subjects not missing any steps), and (f) two point discrimination (where all subjects performed the task successfully). To summarize, the study did not reveal evidence for neurological deficits by any of the TMS coils (see Supplementary material, Statistics S3 and Table S2).

3.1.4. Perceived headache

None of the TMS coils caused perceived headaches (see Supplementary material, Statistics S4 and Figure S2.)

3.2. Computerized cognitive assessment (the CANTAB test battery)

Only *treatment* main-effects and interactions are discussed below. For a statistical analysis of CANTAB *frequency* main-effects, see Supplementary material, Statistics S5.

No significant adverse *treatment* effects were observed in any of the cognitive tests, except for a transient effect in the *Spatial recognition memory* (SRM) task in the *H*1-coil group. This effect was observed only after the first exposure to TMS (single pulses). On the other hand, a cognitive improvement was induced in the *Spatial working memory* (*SWM*) task in the *H*2-coil group but not in the other TMS or sham TMS groups.

3.2.1. Reaction time (RTI)

The ANOVAs conducted for each of the measures did not reveal any significant *treatment* effects [$F(3,27) = 0.073$, n.s; $F(3,27) = 0.612$, n.s.; $F(3,27) = 0.907$, n.s.; $F(3,27) = 1.349$, n.s., for the S*imple reaction time*, *simple movement time, five-choice reaction time and five-choice movement time*, respectively] or interaction effects (Fig. 2). Since the RTI test was conducted in two steps (*simple* and *five-choice*), the results were separately analyzed:

(1) *Stimulus appearing on the touch screen in one location*: There were no *treatment* main-effects or interactions in this task.
(2) *Stimulus appearing in any one of five locations*: The ANOVA for *five-choice movement time* showed no *treatment* effect, but a *treatment* × *frequency* interaction [$F(6,52) = 2.397$, $p < 0.05$]; *H*1-coil subjects decreased their five-choice movement time in the 10 Hz session [compared to the single pulses session; $t(7) = 2.515$, $p < 0.05$]; however, there was no significant difference between the 20 Hz and 10 Hz sessions [$t(7) = -1.362$, n.s.]. Note that this is a long-term effect, appearing 48 h after the single pulses treatment. All other treatment groups (figure-8, *H*2-coil and sham-coil TMS) did not show changes in movement times. After correction for multiple comparisons, the faster movement time induced in the *H*1-coil group is considered a trend only, and not significant ($p > 0.01$). There were no other *treatment* main-effects or interactions (Fig. 2).

3.2.2. Pattern recognition memory (PRM)

Percent of correct responses in the PRM task showed a ceiling effect, limiting the ability to find possible significant effects of the TMS coils. Analysis was therefore conducted on the *latencies for correct responses in the PRM task* (mean time to respond correctly). No significant *treatment* effect [$F(3,27) = 1.161$, n.s.] or interactions were observed (see Supplementary material, Figure S3).

3.2.3. Spatial recognition memory (SRM)

No significant *treatment* effect [$F(3,28) = 0.385$, n.s.] was observed in the *percent of correct responses* (Fig. 3). However, MANOVA revealed a *treatment* × *pre–post* interaction [$F(3,28) = 3.253$, $p < 0.05$].

An additional MANOVA was conducted following the significant interaction observed: (1) *Single pulses TMS session*: The MANOVA revealed no significant main-effects (not shown), but a *treatment* × *pre–post* interaction [$F(3,28) = 3.253$, $p < 0.05$]; the % of correct responses in the *H*1-coil group was significantly reduced right after the single pulses treatment [$t(7) = 5.198$, $p < 0.01$]. There was no difference in the other treatment groups (*H*2-coil, figure-8 and sham-coil).

Therefore, the *H*1-coil group subjected to single pulses transiently decreased performance in the SRM task after stimulation (Fig. 3). This effect was transient, as evident in their return to normal performance prior to the 10 Hz TMS evaluations. Furthermore, there were no changes after the 10 or 20 Hz sessions.

3.2.4. Spatial memory span (SSP)

The critical measure in this test was the *maximal span length* (i.e. the longest sequence successfully recalled by the subject). There were no significant *treatment* effects or interactions. There seems to be a "ceiling effect", limiting the ability to find possible significant effects of the TMS coils (Fig. 4a).

An additional ANOVA was conducted for the *number of test sessions to reach optimal span length* (9 blocks). As each CANTAB test was given to each subject six times (once before and once after each TMS session, on each of the

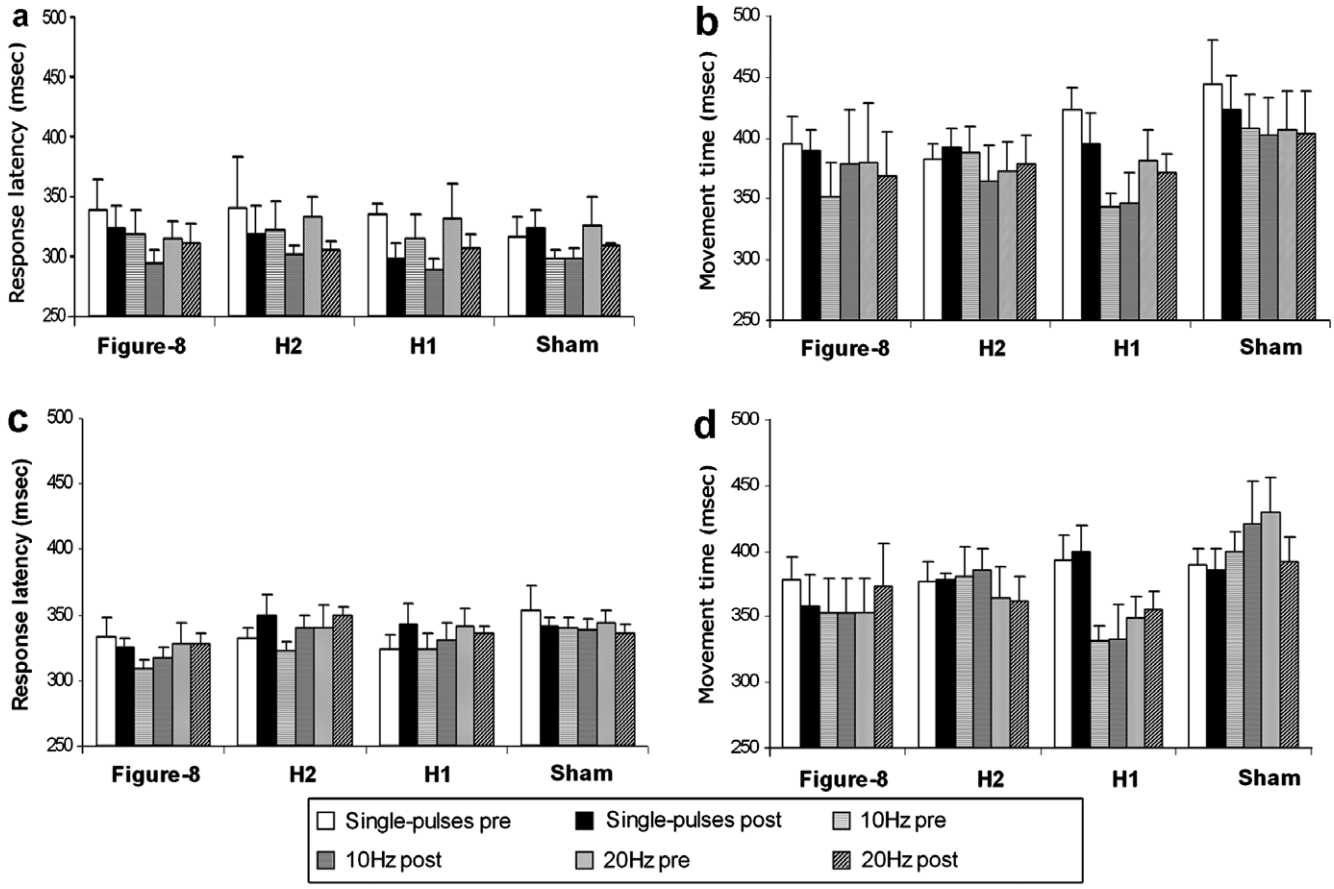

Fig. 2. Reaction time (RTI) in the CANTAB. Panels a and b (simple): Stimulus appears in one location, subject must release press pad and then touch stimulus. No significant *treatment* effect was observed. Panels c and d (five-choice): Stimulus appears in one of five locations; subject must release press pad and then touch stimulus. No significant *treatment* effect was observed, but in the five-choice task, H1-coil subjects tend to show a steeper learning curve ($p < 0.05$). Mean ± SEM RTI scores are presented for the four treatment groups (*H*1-coil, *H*2-coil, figure-8 and sham-coil), pre and post the three TMS visits (single pulses, 10 Hz and 20 Hz). (a) Simple reaction times; (b) simple movement times; (c) five-choice reaction times; (d) five-choice movement times.

three intervention days), subjects generally improved from one test session to the next. Subjects who did not reach the maximal span length, even on the last test session, received a score of 7 (max. no. sessions + 1). The ANOVA revealed a *treatment* effect [$F(3,27) = 4.146$, $p < 0.05$]; a Scheffe post-hoc analysis indicated that subjects treated with the *H*2-coil needed fewer test sessions (trials) to reach the optimal span length of 9 blocks compared to figure-8 or sham coil treated subjects (however, there was no significant difference between *H*2-coil and *H*1-coil subjects). After correction for multiple comparisons, this effect of the *H*2-coil is not considered significant (Fig. 4b).

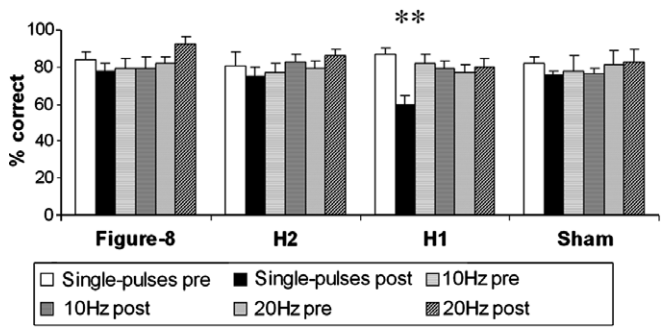

Fig. 3. Spatial Recognition Memory (SRM) in the CANTAB. Percentages (Means ± SEMs) of the correct responses are presented for the four treatment groups in the SRM task, pre and post each TMS session (single pulses, 10 Hz and 20 Hz). The *H*1-coil group subjected to single pulses transiently decreased performance in the SRM task after stimulation ($^{**}p < 0.01$). The transience of this effect is evident in the return to normal performance prior to the 10 Hz TMS evaluations and the lack of effect after the 10 or 20 Hz sessions.

3.2.5. Spatial working memory (SWM)

The MANOVA for *total errors* showed a *treatment* main-effect [$F(3,27) = 3.070$, $p < 0.05$]; Scheffe post-hoc analysis revealed differences between *H*2-coil subjects and sham-coil/figure-8 coil subjects, with *H*2-coil subjects performing fewer errors. The effect was qualified by *treatment* × *frequency*, *treatment* × *pre–post* and *treatment* × *frequency* × *pre–post* interactions [$F(6,52) = 3.772$, $p < 0.01$; $F(3,27) = 2.983$, $p < 0.05$; $F(6,52) = 2.603$, $p < 0.05$; respectively]; *H*2-coil subjects showed a *significant* decrease in error rates after the single pulse TMS session [comparing before and

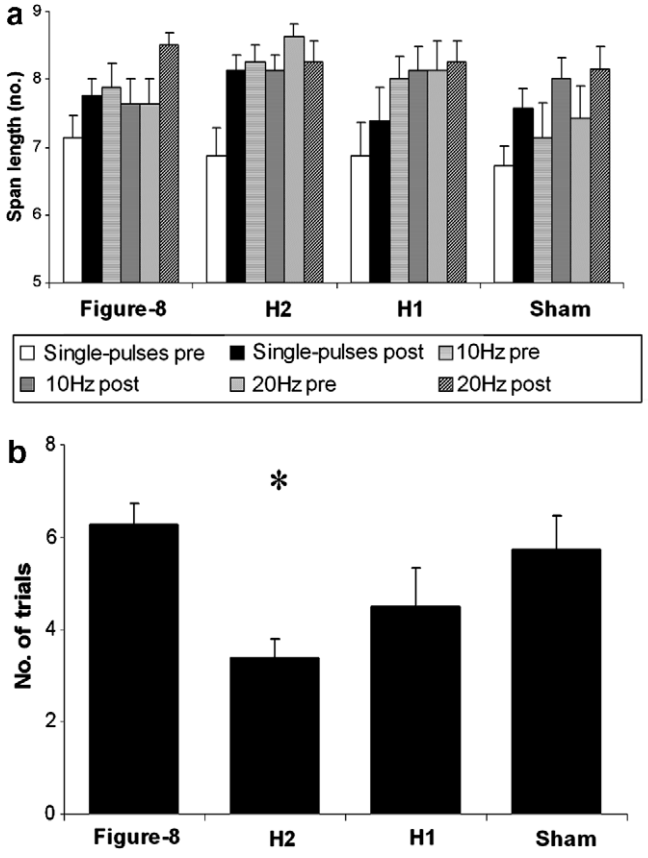

Fig. 4. Spatial Span (SSP) in the CANTAB. (a) *Maximal span length* is the longest sequence successfully recalled by the subject. Mean ± SEM SSP length scores are presented for the four treatment groups, pre and post the three treatment visits (single pulses, 10 Hz and 20 Hz). There were no treatment effects. (b) Number of test sessions (''trials'') to reach optimal span length (9 blocks) in the SSP task is presented as mean ± SEM for the four treatment groups. Subjects treated with the *H*2-coil showed a trend to require progressively fewer test sessions to reach the optimal span length ($^{*}p < 0.05$).

after the first session with the *H*2-coil; $t(7) = 9.296$, $p < 0.001$], with *error rates remaining low* in the following testing sessions (using 10 Hz and 20 Hz). Sham-coil, *H*1-coil and figure-8 coil subjects showed a more varied pattern, indicating some learning but slower and less stable compared to that of the *H*2-coil (Fig. 5).

3.3. Emotional evaluation

Only *treatment* main-effects and interactions are discussed below. For a statistical analysis of PANAS *frequency* main-effects, see Supplementary material, Statistics S6.

PANAS items were grouped according to the positive and negative affect (PA/NA) scales, with each scale expressing the mean score for the corresponding 10 items in the questionnaire.

3.3.1. Positive-Affect scale (PA scale)

The ANVOVA for the positive-affect scale (PA scale) in the PANAS questionnaire (pre and post each stimulation session) found that the different treatments did not differentially affect subjects' positive mood, as evident by no significant *treatment* effects [$F(3,27) = 0.594$, n.s.] or *treatment* interactions (Fig. 6a).

Next, the PA scale scores at the beginning of the study were compared to their PA scale 24–36 h after the last TMS treatment. The ANOVA revealed no significant *treatment* effect [$F(3,27) = 1.863$, n.s.], but a trend for *treatment* × *pre–post* interaction [$F(3,27) = 4.063$, $p < 0.05$]; subjects treated with the *H*1-coil increased their positive-affect between the two measurements [$t(7) = -2.498$, $p < 0.05$], while all other treatment groups showed no changes in their PA scores (Fig. 6b). After correction for multiple comparisons, this effect was not considered significant.

3.3.2. Negative-Affect scale (NA scale)

The ANVOVA for the negative-affect scale (NA scale) in the PANAS questionnaire revealed no significant *treatment* effect [$F(3,26) = 1.138$, n.s.]. Nevertheless, trends for *treatment* × *pre–post* and *treatment* × *freq* × *pre–post* interactions [$F(3,26) = 2.987$, $p < 0.05$; $F(6,50) = 2.317$, $p < 0.05$; respectively] were found. Follow-up analysis indicated no significant differences in the four treatment groups, although there were some non-significant trends indicating that subjects treated with the *H*1-coil tended to report lower negative affect after the 20 Hz session, compared to pre-stimulation reports [$t(6) = 2.320$, $p = 0.059$]. Subjects treated with the figure-8 coil tended to report lower negative affect after the single pulses and the 10 Hz sessions, compared to the pre-stimulation reports [$t(7) = 2.354$, $p = 0.051$, for single pulses; $t(7) = 2.254$, $p = 0.059$; for 10 Hz] (see Supplementary material, Figure S4A).

Next, the NA scale scores at the beginning of the study were compared to the NA scale 24–36 h after the last TMS session. The ANOVA revealed no significant *treatment* effect [$F(3,26) = 0.720$, n.s.]. However, there was a trend

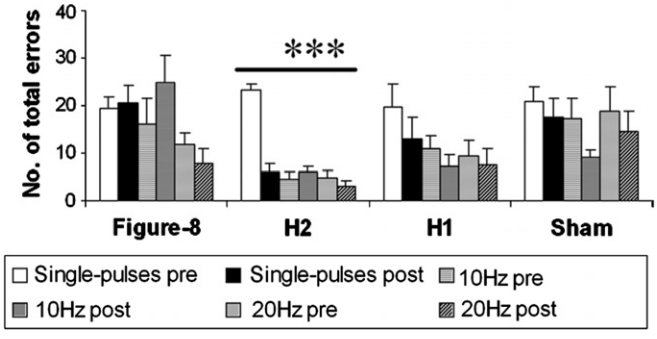

Fig. 5. Spatial Working Memory (SWM) task in the CANTAB. Means ± SEMs of the total errors in the SWM task are presented for the four treatment groups, pre and post each TMS session (single pulses, 10 Hz and 20 Hz). Subjects treated with the *H*2-coil had significantly fewer errors in the spatial working memory task, evident after the single pulse TMS session ($^{***}p < 0.001$), with *error rates remaining low* in the subsequent testing sessions (10 Hz and 20 Hz).

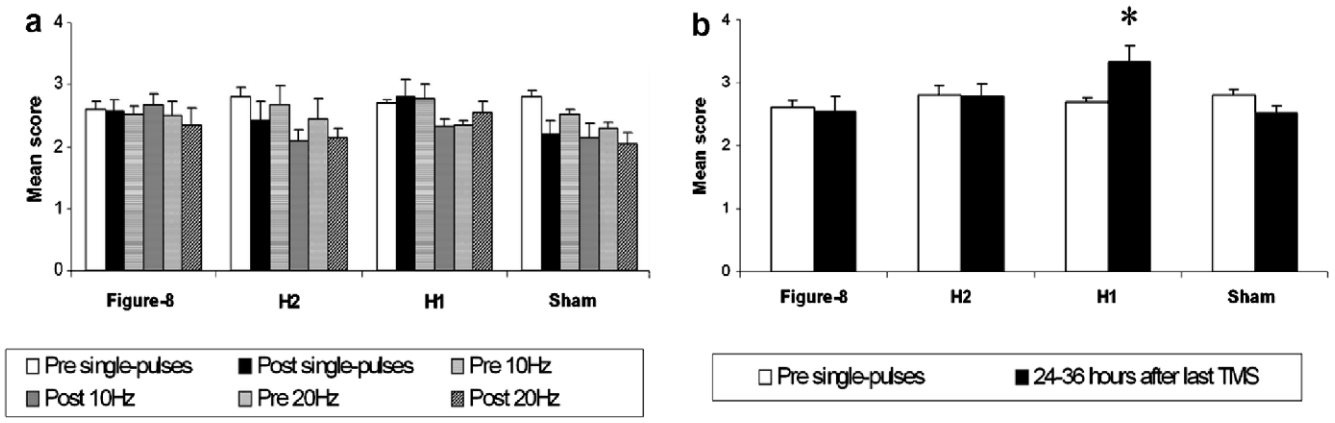

Fig. 6. PANAS positive-affect items. Means ± SEMs of PANAS scores are presented for the four treatment groups (*H*1-coil, *H*2-coil, figure-8 and sham-coil). Panel a shows positive-affect (PA) scores pre and post all three TMS sessions (single pulses, 10 Hz and 20 Hz). Subjects' positive mood was not differentially affected immediately after treatment. Panel b shows the initial PA scores (measured before the single pulses TMS session), compared to the PA scores 24–36 h after the last (20 Hz) TMS session. Subjects treated with the *H*1-coil reported increased positive-affect 24–36 h after the last (20 Hz) session, a trend not observed with any of the other coils ($^{*}p < 0.05$).

for a *pre–post* effect, with subjects reporting lower negative affect after stimulation [$F(1,26) = 6.747$, $p < 0.05$] without *treatment* × *pre–post* interaction [$F(3,26) = 0.837$, n.s.], suggesting that the coils did not differentially effect the negative-affect scores (see Supplementary material, Figure S4B).

4. "Dizzy" and "detachment" scores

The additional two items added to the PANAS specifically for the current study ('detached' and 'dizzy') were analyzed separately.

There were no differential changes in the '*dizzy*' score [a feeling of dizziness] in the different TMS or sham coil groups. The ANOVA showed no *treatment* main-effect [$F(3,26) = 0.439$, n.s.] or *treatment* interactions. Some subjects treated with an *H*-coil (either active or sham) reported feeling slight 'dizziness' immediately after the first TMS session (Single Pulses) (Fig. 7a), a feeling that was gone a few minutes later in both the sham and the active TMS groups. The effect was not found for the *H*-coil groups after 10 Hz or 20 Hz stimulation (not after active nor after sham stimulation).

An additional analysis comparing the 'dizzy' score before the first stimulation and 24–36 h after the last stimulation showed no *treatment* main-effect or *treatment* × *pre–post* interaction [$F(3,26) = 1.204$, n.s.; $F(3,26) = 0.234$, n.s.; respectively] (Fig. 7b).

The '*detachment*' [a feeling of dissociation] score, which was the second item added to the PANAS, showed a *significant treatment* effect [$F(3,26) = 8.202$, $p < 0.001$]; post-hoc Scheffe test indicated that *H*1-coil subjects reported more feelings of detachment compared to subjects treated with the sham-coil, the figure-8 coil or the *H*2-coil. The main-effect was qualified by a *significant treatment* × *pre–post* effect [$F(3,26) = 15.526$, $p < 0.001$]; only *H*1-coil subjects showed an increase in feelings of detachment from before the first stimulation and 24–36 h after the last stimulation [$t(6) = -5.258$, $p < 0.01$] (Fig. 8).

5. Discussion

This study is the first to evaluate the safety of deep TMS. The study also revealed some cognitive effects of deep (but not standard) TMS of the prefrontal cortex. Stimulation parameters used in the present study are similar to those used with standard TMS for the treatment of depressive disorders. Deep TMS over the left prefrontal cortex of healthy volunteers was found to be safe, without any episodes of seizures and without signs of adverse cognitive or emotional effects.

Numerous earlier safety studies of standard TMS have not found significant signs of neuropsychological disturbances, or changes in auditory thresholds, after 2–4-week courses of rTMS (Padberg et al., 1999; Hausmann et al., 2000; Loo et al., 2001; Shajahan et al., 2002; Martis et al., 2003; O'Connor et al., 2003; Januel et al., 2006; Rachid and Bertschy, 2006). In this study, no hearing loss was found in any subject. Nor was there evidence that any of the TMS coils induced hemodynamic abnormalities, or neurological deficits. Previous studies indicate that rTMS often induces mild headaches and that this may result from the need to hold the head steady for several minutes during the treatment (Machii et al., 2006). However, the present study did not find perceived headaches caused by any of the TMS coils, even though each session was 14 min long.

Some subjects treated with the *H*-coils (including the *sham H*-coil) reported feeling slightly dizzy immediately after the first TMS treatment; the dizziness disappeared within minutes. The CANTAB measures did not detect any acute signs of adverse cognitive effects of either deep or standard TMS over the prefrontal cortex, except for a transient short-term effect of the *H*1-coil on *Spatial recognition memory (SRM)* on the first day of rTMS only but

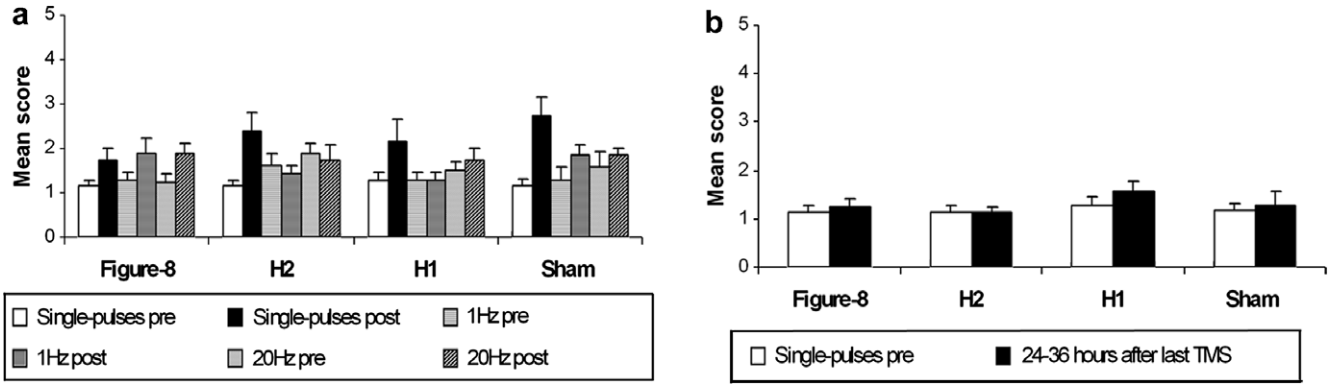

Fig. 7. 'Dizzy' item added to the PANAS. Means ± SEMs scores for 'dizzy' are presented for the four treatment groups. (a) Pre and post all the three TMS session (single pulses, 10 Hz and 20 Hz). (b) Scores of the pre single pulses TMS session compared to scores obtained 24–36 h after last (20 Hz) TMS session.

not in the following treatment days. The standard emotional questionnaires did not detect any acute signs of adverse emotional effects.

In addition, while stimulation with the standard figure-8 coil did not significantly affect cognitive abilities and subjective emotional reports relative to sham conditions, a cognitive improvement in *Spatial working memory (SWM)* was induced by deep TMS using the *H*2-coil.

The CANTAB *Reaction Time* (*RTI*) findings indicate that the coils did not affect differentially the reaction times of the subjects, and hence most likely their processing speed (since these measures do not have a significant motor component). However, when analyzing the subjects' motor performance, the coils show a differential effect, more evident when the stimulus appears in one of five locations. In the *five-choice* task, the cognitive load is larger. The fact that the *H*1-coil subjects tend to show a steeper learning curve in these conditions (evident more clearly between the single pulses TMS stimulation and 10 Hz stimulation) may indicate a facilitation effect induced by deep ventrolateral prefrontal regions (Roth et al., 2007).

The only negative effect observed in the CANTAB battery was that of the *H*1-coil in the *Spatial recognition memory* (*SRM*) task after the single pulses session (but not the 10 Hz or 20 Hz sessions), which induced a transient reduction in performance. This significant transient effect may possibly be explained as a novelty effect unique to the *H*1-coil. Each subject was TMS-naïve at the time of the Single Pulses session, which was always the first TMS treatment. Due to potential novelty effects, Sommer et al. (2002), recommends discarding the first day's results of TMS-naïve subjects (Sommer et al., 2002). This novelty explanation is supported by the fact that the decreased performance in this task was not noted before (or after) the next TMS sessions. Alternatively, this may be a negative effect of single pulses using the *H*1-coil over the prefrontal

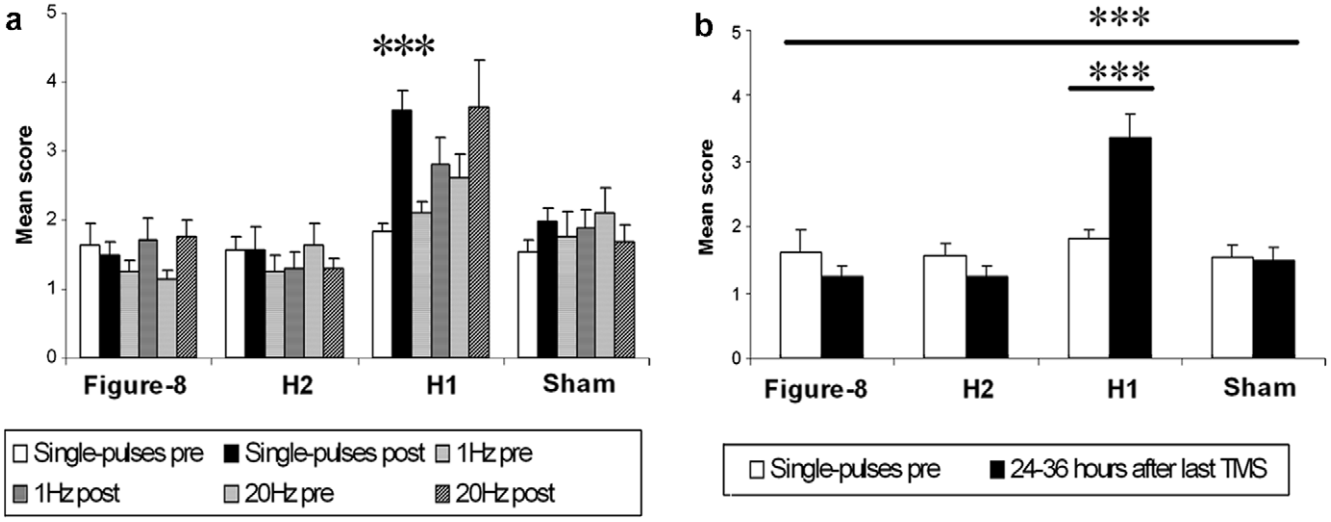

Fig. 8. 'Detachment' item added to the PANAS. Means ± SEMs scores for '*detached*' are presented for the four treatment groups. (a) Pre and post all the three TMS session (single pulses, 10 Hz and 20 Hz). (b) Scores of the pre single pulses TMS session compared to scores obtained 24–36 h after the last (20 Hz) TMS session. Subjects treated with the *H*1-coil reported increased 'detachment' [a feeling of dissociation] after stimulation, an effect evident even 24–36 h after last stimulation (***$p < 0.001$).

cortex. This transient phenomenon requires further investigation using an appropriate design using repeated sessions of single pulses.

On the other hand the *H*2-coil induced improvement in *Spatial working memory* (*SWM*) tasks after the single pulses session (as indicated by the decrease in number of errors). Subjects treated with the *H*2-coil had significantly fewer errors in this task, with *error rates remaining low* in the subsequent testing sessions (10 Hz and 20 Hz). The higher error rates in the sham coil group indicate that the *H*2-coil improvement in error rates was not due to a practice effect. The *H*2-coil treatment in the first TMS session caused a long-term improvement which lasted for at least two days before the 10 Hz treatment. Furthermore, *H*2-coil error rates in SWM were consistently lowest throughout the sessions. These results in the SWM task indicate an improvement in frontal lobe functions, especially the ventrolateral prefrontal cortex (Robbins et al., 1994), induced by the *H*2-coil. Some tendency for improved spatial memory was also observed for the *H*1-coil group, but this was not significant, indicating that deep bilateral (*H*2) prefrontal cortex stimulation may be more effective than deep stimulation preferentially over the left (*H*1) prefrontal cortex (Roth et al., 2007).

Subjects treated with the *H*1-coil reported increased positive-affect 24–36 h after the last (20 Hz) TMS session. However, after correction for multiple comparisons, this effect was not considered significant. Subjects treated with the *H*1-coil also reported an increased feeling of '*detachment*' that was evident even 24–36 h after the last stimulation. The 'detachment' feeling of subjects added to the PANAS questionnaire in the present study is not a standard measure and has not been validated. Recent literature, however, indicates a role for the prefrontal cortex and especially the ventral part of the prefrontal cortex (which can be affected directly by the *H*-coils but not by the figure-8 coil) in "self awareness" and the "default-mode" (resting) network (Gusnard et al., 2001; Raichle et al., 2001; Wicker et al., 2003). It is possible that the deep (but not the superficial) stimulation over the prefrontal cortex interfered with this circuit inducing the highly significant increases in 'emotional detachment' reported. This observation requires further investigation using an appropriate design and a battery of tests for measuring dissociation and self awareness (while the present study was primarily designed for safety evaluations of deep TMS).

The emotional effects of rTMS observed *24–36 h after the last* (*20 Hz*) *session* are quite surprising, but similar effects are observed in several clinical studies (e.g. depressive patients) where there are no obvious acute effects, but emotional changes are observed later on. A potential mechanism for such late effects might be some feedback mechanism related to long-term synaptic plasticity induced after the stimulation.

After the Single Pulses (first TMS) treatment only, subjects given any *H*-coil treatment (including *sham H*-coil) reported feeling slightly '*dizzy*' (a question added to the PANAS test). The "PANAS" questionnaire was given right after the TMS session. A short interview about body sensations, weakness or dizziness several minutes later (before subjects went home) showed that this effect was gone. Furthermore, this effect was not evident in later deep TMS sessions in the same subjects (after 10 Hz or 20 Hz). It is possible that the placement of the H-coils (including the sham H-coil) on the scalp for about 15 min (held in a fixed position within a large head covering) induces some dizziness, as expressed after the first experience, for a few minutes, while in later sessions subjects become habituated to the setup.

Large interindividual variations have been observed in previous rTMS studies (Maeda et al., 2000; Peinemann et al., 2000; Wu et al., 2000; Romero et al., 2002; Daskalakis et al., 2006). Could the cognitive and emotional changes be simply the result of interindividual variability? If that were true, one would expect to also find changes as a result of standard TMS. Yet significant changes were only observed in subjects treated with Deep rTMS (either the *H*1-coil or the *H*2-coil). (See Table 3.)

It is important to note that great care was taken in the present study to blind both subjects and psychological testers with respect to the type of TMS coil used. However, it is likely that the subject was clearly aware of the switch from single pulses to 10 Hz, but less aware of the switch to 20 Hz. So differences between single pulses and higher frequencies were more obvious and may have affected the subjects' behavior afterwards. Nevertheless, training effects, discussed below, were probably more influential.

There is, however, one limitation of the present study – shared up to now by almost all TMS studies. The person administering the TMS treatment is not blind to which treatment coil is being used. It is possible that some subtle psychological influence may have affected the cognitive or emotional results.

Given that each CANTAB test was given to each subject six times, before and after each TMS intervention, on each of the three intervention days, it is likely that training effects were observed. Parallel versions of the CANTAB tests were not used on retesting. Improved performance with successive TMS days was found on several tests, even when the subject was treated with the sham coil. Therefore most measures suffer from "practice effects", while the Single Pulses treatment results are 'clean'. In some cases a "floor effect" (e.g., in number of errors in the Spatial Working Memory task), or a "ceiling effect" (e.g., in span length in the Spatial Span task), was reached due to the "practice effects" of the tests. Therefore, it is hard to draw conclusions about improvements under 10 Hz and 20 Hz, even though it was clear that both 10 Hz and 20 Hz were safe. The fact that some cognitive or emotional effects were found with single pulses but not with 10 or 20 Hz does not mean that 10 or 20 Hz would be less effective if given first.

The above discussion raises the question of how deep TMS might have affected the brain. Maps of the regions stimulated with deep TMS were described in detail recently

Table 3
Cognitive and emotional testing – some effects

Cognitive or emotional parameter	Figure-8	*H*1-coil	*H*2-coil	Sham *H*-coil
CANTAB – Reaction time (RTI) (Fig. 2)	n.s.	A trend for a steeper learning curve especially in the *five-choice* task	n.s.	n.s.
CANTAB – Pattern recognition memory (PRM) (Supplementary material, Figure S3)	n.s.	n.s.	n.s.	n.s.
CANTAB – Spatial recognition memory (SRM) (Fig. 3)	n.s.	Transient decrease in performance after single pulses only	n.s.	n.s.
CANTAB – Spatial memory span (SSP) (Fig. 4)	n.s.	n.s.	A trend for a steeper learning curve	n.s.
CANTAB – Spatial working memory (SWM) (Fig. 5)	n.s.	n.s.	Significant decrease in error rates	n.s.
PANAS – Emotional parameters – positive affect (Fig. 6)	n.s.	A trend for increased positive-affect 24–36 h after the last (20 Hz) session	n.s.	n.s.
PANAS – Emotional parameters – negative affect (Supplementary material, Figure S4)	n.s.	n.s.	n.s.	n.s.
Emotional parameters – "dizzy" (Fig. 7)	n.s.	Immediately after single pulses (only) some felt transiently 'dizzy'	Immediately after single pulses (only) some felt transiently 'dizzy'	Immediately after single pulses (only) some felt transiently 'dizzy'
Emotional parameters – "detachment" (Fig. 8)	n.s.	Significantly increased 'detachment' after stimulation, evident even a day after the last stimulation	n.s.	n.s.

n.s. – not significant.

(Roth et al., 2007). In the present study the coil was placed over the prefrontal cortex. According to our phantom brain measurements (Roth et al., 2007), using 110% of motor threshold over this region allows *direct* stimulation of much deeper portions of the prefrontal cortex, but not subcortical regions. Nevertheless previous imaging studies demonstrated that even with standard TMS (using the figure-eight coil), several deeper cortical and subcortical regions can be activated due to brain connectivity (Denslow et al., 2005; Luborzewski et al., 2007). It is therefore necessary to combine deep TMS and imaging studies in order to suggest or speculate on the mechanism of the cognitive and emotional effects observed in the present study. Our phantom brain measurements indicate that, using the intensities similar to those of the present study, both the *H*1 and the *H*2 coils induce direct stimulation in both dorsal and ventrolateral portions of the PFC (in depths of up to 3.5 cm within), while stimulation with the figure-eight coil induces direct stimulation of some portion of the dorsolateral PFC (up to 1.0 cm in depth) only (Roth et al., 2007). Therefore, the cognitive and emotional effects of direct stimulation of deeper PFC regions observed in the present safety study suggest that ventral and especially ventrolateral portions of the PFC play important roles in spatial memory and perhaps mood and self-awareness. These effects will be further studied in appropriate studies designed for such questions.

The present study, involving 31 subjects including 16 who received stimulation with deep TMS coils (*H*1 or *H*2) using frequencies of up to 20 Hz (and a total of 840 pulses within 15 min), indicates that deep TMS is safe under these conditions. The potential of the *H*-coils to directly reach deeper brain regions provides an opportunity for numerous research and clinical applications. Deeper brain regions, such as the ventral prefrontal cortex and its connections to the nucleus accumbens and ventral tegmentum, are associated with reward and motivation. Stimulating these deeper regions may be beneficial for the treatment of depression, addiction, schizophrenia and other psychiatric and neurological disorders. The cognitive and emotional effects induced by deep rTMS, but not by standard or sham rTMS, of the prefrontal cortex, are the first indications for transient effects of deep rTMS on human higher brain function.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2007.09.061.

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