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Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-Coil

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Abstract

Objective: Standard coils used in research and the clinic for noninvasive magnetic stimulation of the human brain are not capable of stimulating deep brain regions directly. As the fields induced by these coils decrease rapidly as a function of depth, only very high intensities would allow functional stimulation of deep brain regions and such intensities would lead to undesirable side effects. We have designed a coil based on numerical simulations and phantom brain measurements that allows stimulation of deeper brain regions, termed the Hesed coil (H-coil). In the present study we tested the efficacy and some safety aspects of the H-coil on healthy volunteers.

Methods: The H-coil was compared to a regular figure-8 coil in 6 healthy volunteers by measuring thresholds for activation of the abductor pollicis brevis (APB) representation in the motor cortex as a function of distance from each of the coils.

Results: The rate of decrease in the coil intensity as a function of distance is markedly slower for the H-coil. The motor cortex could be activated by the H-coil at a distance of 5.5 cm compared to 2 cm with the figure-8 coil.

Conclusions: The present study indicate that the H-coil is likely to have the ability of deep brain stimulation and without the need of increasing the intensity to extreme levels that would cause a much greater stimulation in cortical regions.

Significance: The ability of non-invasive deep brain stimulation potentially opens a wide range of both research and therapeutic applications.
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Keywords: Transcranial magnetic stimulation; Deep brain stimulation; Magnetic coil; Motor threshold; Electric field

1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique used to apply magnetic pulses to the brain. The pulses are administered by passing high currents through an electromagnetic coil placed upon the scalp that can induce electrical currents in the underlying cortical tissue, thereby producing a localized axonal depolarization. TMS has become a major tool in brain research and, potentially, a promising treatment for various neurobehavioral disorders (Kircaldie et al., 1997; Wassermann and Lisanby, 2001). The coils used for TMS (round or figure-of-eight shaped) induce stimulation in cortical regions mainly just superficially under the windings of the coil. The intensity of the electric field drops dramatically deeper in the brain as a function of the distance (Cohen et al., 1990; Eaton, 1992; Maccabee et al., 1990; Tofts, 1990; Tofts and Branston, 1991). Therefore, to stimulate deep brain regions, a very high intensity would be needed. Such intensity cannot be reached by standard magnetic stimulators using the regular figure-of-eight or circular coils. Moreover, the intensity needed to stimulate deeper brain regions effectively would stimulate cortical regions and facial nerves over the level that might lead to facial pain, facial and cervical muscle contractions, and other undesirable side effects.

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Recently, we have developed a new coil, termed the Hesed Coil (H-coil), that enables effective stimulation of deep brain regions, without inducing a much greater stimulation of superficial cortical regions (Roth et al., 2002). The H-coil was designed based on numerical calculations and was optimized according to measurements of the induced electric fields in a phantom brain.

Physiological studies of peripheral nerves revealed that optimal activation occurs when the field is oriented in the same direction as the nerve fiber (Basser and Roth, 1991; Duran et al., 1989; Roth and Basser, 1990). Hence, in order to stimulate deep brain regions, it is necessary to use coils in such an orientation that they will produce a significant field in the preferable direction to activate the neurons under consideration.

In the present study we tested the biological efficacy of the H-coil, using the motor threshold as a measure of a biological effect. The rate of decrease of the electric field as a function of distance from the coil was measured by gradually increasing the distance of the coil from the skull and measuring the motor threshold at each distance. A comparison was made to the figure-8 coil.

2. Methods

2.1. Subject

Six healthy, right-handed volunteers (4 men and 2 women, mean age 36 yr, range 25–45 yr) gave written informed consent for the study, which was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board. Subjects were interviewed and examined by a neurologist and found to be free of any significant medical illness or medications known to affect the CNS.

2.2. TMS coils

The TMS coils used in this study were a specific version of the H-coil and a figure of eight coil. The H-coil version used in this study allows a comfortable placement above the hand motor cortex. The theoretical considerations and design principles of the H-coils are explained in our previous study (Roth et al., 2002). In short, the coil is designed to generate summation of the electric field in a specific brain region by locating coil elements at different locations around this region, all of which have a common current component which induce electric field in the desired direction (termed $+z$ direction). In addition, since a radial component has a dramatic effect on electric field magnitude and on the rate of decay of the electric field with distance, the overall length of coil elements which are nontangential to the skull should be minimized, and these elements as well as coil elements having current component in the opposite direction ($-z$ direction) should be located as distant as possible from the brain region to be activated.

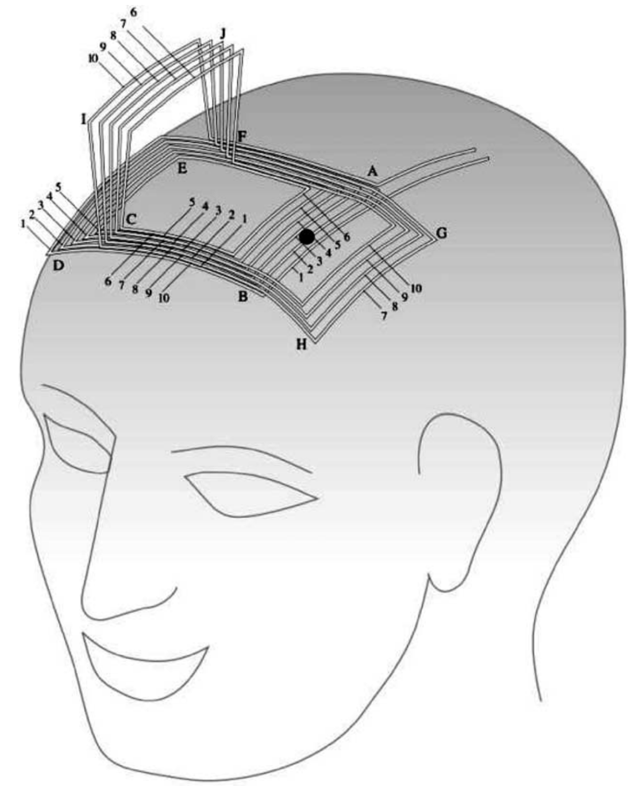

Fig. 1. Sketch of the H-coil version used in this study placed on a human head. The coil orientation shown in the figure is designated for optimal stimulation of the right APB (indicated by a black spot). Coil details are explained in Section 2.

The H-coil version used in the present study is shown in Fig. 1. The coil has 10 strips carrying a current in a common direction ($+z$ direction) and located around the desired motor cortex site (segments A–B and G–H in Fig. 1). The average length of the strips is 11 cm. The only coil elements having radial current components are those connected to the return paths of five of the strips (segments C–I and J–F in Fig. 1). The length of these wires is 8 cm. The return paths of the other five strips are placed on the head at the contralateral hemisphere (segment D–E in Fig. 1). The wires connecting between the strips and the return paths (segments B–C and F–A in Fig. 1) are on average 9 cm long.

The H-coil was compared to a standard commercial Magstim figure-of-8 coil with internal loop diameters of 7 cm.

2.3. Experimental setup

Subjects were seated with the right forearm and hand supported. Motor evoked potentials (MEPs) of the right abductor pollicis brevis (APB) muscle were recorded using silver–silver chloride surface electrodes. Subjects were instructed to maintain muscle relaxation throughout the study. EMG amplitude was amplified using a conventional

EMG machine (Counterpoint, Dantec Electronics, Skovlunde, Denmark) with band-pass between 10 and 2000 Hz. The signal was digitized at a frequency of 5 kHz and fed into a laboratory computer.

A Magstim Super Rapid stimulator (The Magstim Company New York, NY), which produces a biphasic pulse, coupled with either the figure-8 coil or the H-coil, was used. Preliminary studies showed the H-coil to have a loudness when activated of 122 dB, similar to other coils used in our laboratory. As standard laboratory practice, subjects were fitted with foam ear plugs to attenuate the sound.

The coil was placed on the scalp over the left motor cortex. The intersection of the figure-8 coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. Thus the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus and therefore optimal for activating the corticospinal pathways transsynaptically (Brasil-Neto et al., 1992; Kaneko et al., 1996). Similarly, the H-coil was placed on the scalp with the handle pointing backward in such a way that center of the strips cover the motor cortex and in such a direction that the current induced in the neural tissue would be perpendicular to the line of the central sulcus. With a slightly suprathreshold stimulus intensity, the stimulating coil was moved over the left hemisphere to determine the optimal position for eliciting MEPs of maximal amplitudes (the ‘hot spot’). The optimal position of the coil was then marked on the scalp to ensure coil placement throughout the experiment. Resting motor threshold was determined to the nearest 1% of the maximum stimulator output and was defined as the minimal stimulus intensity required to produce MEPs of >50 μV in ≥ 5 of 10 consecutive trials at least 5 s apart.

The coils were held in a stable coil holder, which could be adjusted at different heights above the ‘hot spot’ on the scalp. The resting motor threshold was determined at different distances above the scalp, using increments of 0.5 cm. Thus, the coil was moved in a radial direction away from the ‘hot spot’ and the threshold was measured for each distance.

2.4. Safety measurements

Since the H-coil was not used in previous clinical TMS studies, we asked the subjects to report any side effects including pain, anxiety or dizziness, changes in mood (Watson et al., 1988) and we performed cognitive and hearing tests before and after the TMS session. For the cognitive testing we used the CalCap computer program to test immediate and delayed memory as described previously (Wassermann et al., 1996).

3. Results

None of the 6 subjects who participated in the study reported any significant side effects after the TMS session. We did not find any change in cognitive or hearing abilities in these 6 subjects. A slight and short lasting headache was reported by 1 out of the 6 subjects. In a different experiment done subsequently, not reported in this manuscript, we used the H-coil to deliver single or paired pulses at 1 Hz during 20 s over five different locations on the scalp in 3 additional subjects. The intensity of stimulation was 120% of motor threshold, the interval between the 20-s trains was 2 min and the total number of trains was 10 for each subject. The third of these subjects experienced some hearing loss in his left ear, a 30 dB loss at 4000 Hz which has been stable for 10 months and appears permanent. The ear protection had fallen out transiently during the study.

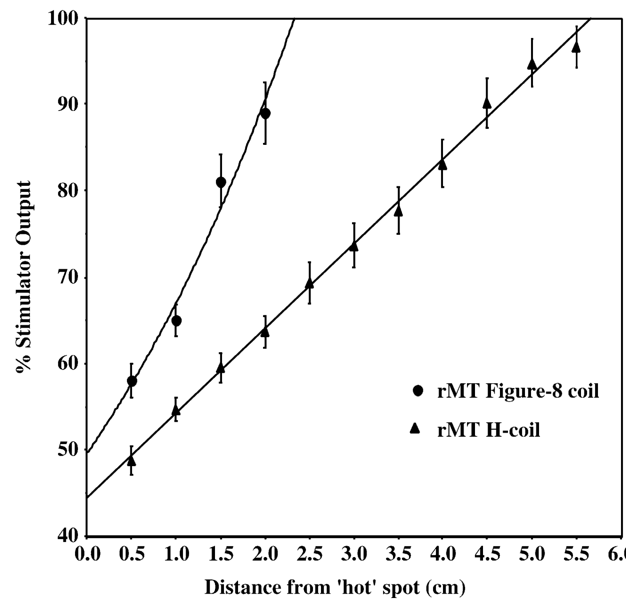

Fig. 2. Intensity needed for APB stimulation at different heights above the scalp. Resting motor threshold of the APB was measured at different distances above the ‘hot spot’ when using either the H-coil or the figure-8 coil. The % of stimulator power needed to reach the resting motor threshold vs. the distance of the coil from the ‘hot spot’ on the skull is plotted. The points represent means and SDs of 6 healthy volunteers.

The percentage of stimulator output required for APB activation by each coil is plotted in Fig. 2 as a function of distance from the ‘hot spot’ on the scalp. It can be seen that the efficacy of the H-coil at large distances from the scalp was significantly greater as compared to the figure-8 coil. When using the maximal stimulation power output, the figure-8 coil can be effective (reach stimulation threshold) up to 2 cm away from the coil, while the H-coil can be effective at 5.5 cm away from the coil. Moreover, the rate of decay of effectiveness as a function of the distance from the coil is much slower in the H-coil relative to the figure-8 coil (Fig. 2).

4. Discussion

The present study confirms our theoretical calculations and phantom brain measurements (Roth et al., 2002) indicating the ability of the H-coil to stimulate brain structures at a large distance from the coil. The comparison between the TMS coils demonstrated a significantly improved depth penetration, and a much slower rate of decay of effectiveness as a function of the distance from the coil, when using the H-coil relative to the regular figure-8 coil. This indicates that when stimulating deep brain regions by using the H-coil, the cortical stimulation is not much higher for the same activation in depth. Nevertheless, it is clear that stimulation of a deep brain region will involve cortical stimulation as well, at regions close to the coil and above the target in depth.

The H-coil produces a summation of the electric field from several coil elements carrying current in the same direction. In contrast, the electric field of the figure-8 coil is produced by a concentrated region in the center of the coil. In addition, the relative fraction of the figure-8 field that is produced by coil elements which are nontangential to skull surface is much larger than in the H-coil. These two reasons lead to the fact that although the figure 8 field is more focal, it has more significant reduction both in absolute field magnitude at any point and in the percentage of a deep region field relative to field at the surface.

In order to reach the stimulation threshold of neurons, a total field of 30–100 V/meter is needed (Kammer et al., 2001), therefore the figure-8 coil would hardly reach the stimulation threshold of the leg motor area, which is about 3 cm in depth, even when 100% of the Magstim stimulator output is used. When using a double cone coil, which produces very strong fields that decay quite fast as a function of distance (Roth et al., 2002), 30–50% of the stimulator output is required to stimulate the leg motor area (Maccabee et al., 1990; Terao et al., 1994, 2000). Such stimulation is painful since a much higher field is induced in higher cortical areas and facial muscles. In order to reach a stimulation threshold at a depth of 4–6 cm, the figure-8 coil would not be sufficient and the double cone coil would cause even greater pain and perhaps other side-effects. According to our calculations and phantom brain measurements (Roth et al., 2002), in order to reach 50 V/m in depth of 5 cm, almost 500 V/m will have to be induced in depth of 1 cm when using the double cone coil while only 100 V/m will be induced when using the H-coil. Therefore, it is likely that excitation threshold can be reached at 4–6 cm using the H-coil without inducing pain and other side-effects. Nevertheless, as the field induced by the H-coil is less focal, it is possible that even the low intensity could produce a greater range of side-effects. In the present study, subjects did not report any special side-effects and there was no change in their cognitive testing.

It should be emphasized that although the structure stimulated in this study was in the motor cortex, and the medium between the coils and the 'hot spot' was mainly air, the rate of decay within the brain itself should be very similar. This is a delicate point that should be elaborated. The electric conductivity of the brain is much greater than that of air. In conductive materials such as the brain, radial current components of the coil would lead to charge accumulation on the surface of the brain, which would cause a decrease of the field in any point inside the brain. Hence, the rate of decay of electric field with distance would be faster in the brain than that measured in air. Nevertheless, the field distribution inside the brain is independent of the location of the interface between the conductive and insulating media (Branston and Tofts, 1990; Eaton, 1992; Tofts, 1990). As a result, the rate of decay within the brain when attaching the coil to the skull would be similar to that measured in this study, where the coil was raised above the skull. Small changes are expected due to the fact that coil configuration relative to the skull is somewhat different when it is raised. The H-coil is designed to minimize radial current components when placed on the head; hence the amount of radial components may be slightly different and probably larger when the H-coil is raised above the head. Therefore, the advantage of the H-coil as compared to the figure-8 coil, in terms of the rate of decay of the field as a function of distance, may be even greater when the coils are placed on the head.

The present study is the first one in which the H-coil was used in humans. Although the H-coil has a remarkable ability to penetrate into deeper brain regions, due to the slower decay of the electric field as a function of distance, none of the subjects in the present study reported any side effects and cognitive or hearing abilities were not affected. Nevertheless, it should be emphasized that subjects in the present study experienced only 20–30 single pulses at intensities greater than those needed for minimal APB activation (when looking for the hot spot for APB activation) and that the rest of the pulses were given just at the minimal level for APB activation when the coil was placed either on the scalp or at different heights above the scalp. Future studies will address the safety and efficacy of the H-coil when used in higher doses. As we have reported, one subject has experienced some hearing loss in a subsequent experiment. Our past safety studies have not demonstrated that hearing loss is to be expected (Pascual-Leone et al., 1992). As the loudness of the H-coil does not appear different from other coils, this result may be due in part to particularly sensitive hearing in this subject and lapse in the hearing protection. However, as we did caution before, the event does emphasize need in all TMS studies to take care to protect hearing.

The H-coil version used in this study was optimized for stimulation of the right APB motor cortex. Modified coil configuration, placement and orientation may be used for stimulation of other neuronal structures. The present study demonstrated the ability of the H-coil to effectively activate brain structures at a large distance from the coil, with a slow rate of decay of electric field with distance. These features of the H-coil may enable stimulation of almost any deep brain region or combination of regions, and thus bear a potential use for a variety of medical and research applications.

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