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Transcranial Magnetic Stimulation of Deep Brain Regions: Principles and Methods

Yiftach Roth^a, Frank Padberg^c, Abraham Zangen^b

^aAdvanced Technology Center, Sheba Medical Center, Tel Hashomer, and ^bThe Weizmann Institute of Science, Department of Neurobiology, Rehovot, Israel; ^cDepartment of Psychiatry and Psychotherapy, Ludwig Maximilian University Munich, Munich, Germany

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is an established technique for noninvasive brain stimulation and widely used in basic and clinical neurophysiology. Yet, brain stimulation using traditional rTMS systems is limited to superficial, i.e. mainly cortical brain sites laying at the outer cerebral or cerebellar convexity and deeper structures are only modulated by transsynaptic effects primarily stimulated regions exert. Here we report recent developments in extending rTMS to deep brain regions. The Heschl coils (H-coils) are a novel development in rTMS, designed to achieve effective stimulation of deeper neuronal regions without inducing unbearable fields cortically, thus broadly expanding the potential feasibility of TMS for research and treatment of various neuropsychiatric disorders. The construction principles and design of the H-coils and phantom measurements and clinical studies are presented comparing the penetration depth of the H-coils and traditional rTMS coils. Using this approach, transcranial stimulation of subcortical white matter tracts, neurons in the mesial temporal lobe and the ventromedial prefrontal cortex together with the adjacent cingulate gyrus will become available. Moreover, the threshold for neuronal activation depends on the duration of the TMS perturbation through a strength-duration curve. Thus, it may theoretically be possible to exploit the temporal characteristics of the neuronal response, in order to improve dramatically the efficacy and focality of the stimulation of deep brain structures, potentially enabling focused stimulation of deep regions with no activation of cortical brain regions. These considerations will be of particular interest for future treatment options in affective disorders, schizophrenia and drug addiction among others.

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Transcranial magnetic stimulation (TMS) is a noninvasive technique used to apply brief magnetic pulses to the brain. The pulses are administered by passing high currents with a stimulator through an electromagnetic coil placed upon the patient's scalp, inducing electric currents in the underlying cortical tissue, thereby producing localized axonal depolarizations. Neuronal stimulation by TMS was first demonstrated in 1985 [1], when a circular coil was placed over a normal subject vertex and evoked action potentials from the abductor digiti minimi. Since then, this technique has become a major research tool in basic and clinical neurophysiology, and has been applied to studying nerve conduction, excitability [2], and functional connectivity in the brain and peripheral nerves. In addition, in recent years, repetitive TMS (rTMS) has become a potentially promising treatment option for various neurobehavioral disorders spanning a wide age range [3–6].

The capacity of TMS to elicit neuronal response has until recently been limited to the cerebral cortex. The coils used for TMS (such as round or figure-of-eight coils) 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 from the coil [7–10]. 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. Stimulation of regions at a depth of 3–4 cm, such as for the primary motor area of the leg, may be achieved using coils such as the double-cone coil [11–13], which is a larger figure-of-eight coil with an angle of about 95° between the two wings. However, 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 may cause epileptic seizures and other undesirable side effects.

The difficulty of efficiently activating deep neuronal structures using TMS emerges from physical properties of the brain, and from physical and physiological aspects of the interaction of a TMS system with the human brain. The purpose of this chapter is to demonstrate how the TMS system, including both the TMS coils and the stimulator, may be optimized for effective stimulation of deeper brain regions. The subsequent section provides neuroanatomical considerations, followed by a section on the basic principles of TMS, a section that describes the construction principles and design of TMS coils for deep brain stimulation, and gives results of clinical studies and phantom measurements obtained with some exemplary coils, and finally a section, in which we outline a method and a TMS system which enable to exploit the temporal characteristics of the neuronal response, in order to improve dramatically the efficiency and focality of stimulation of deep brain structures.

Neuroanatomical Considerations

In the brain, TMS acts on neuronal activity within a three-dimensional neuronal network. Looking at the cortical level, the cytoarchitecture varies between different brain regions, and even the single cerebral lobes, e.g. the frontal lobe, consist of regions with distinct structural differences: e.g. the primate's prefrontal cortex is a homotypical isocortex, clearly laminated, with a well-developed internal granular layer (IV) that differentiates it from the rest of the frontal cortex [14]. This layer becomes thicker and more distinct on approaching the frontal pole, although the cortex as a whole becomes thinner.

Another issue to be considered is the orientation of the magnetic field in relation to the cortical folding. The coil position in relation to the individual gyri and sulci matters for stimulation effects as demonstrated for the primary motor cortex where the orientation of the current flow in relation to the central sulcus changes the amplitude of motor evoked potentials [15]. Moreover, TMS of the motor cortex can evoke D-waves, representing direct stimulation of the corticospinal axon, as well as I-waves that arise from transsynaptic activation of corticospinal neurons [16, 17]. Thus, both corticospinal neurons and interneurons may be stimulated simultaneously. D-waves may be predominantly elicited in corticospinal fibers running horizontally in the primary motor cortex in a direction at right angles to the central sulcus. Accordingly, for intrinsic hand muscles, the motor cortex is excited most readily by coil currents running at right angles to the axis of the precentral gyrus [17]. Presumably, the excitation occurs at the site where the corticospinal fibers bend down into the central sulcus [18]. Therefore, neuronal stimulation will depend on the position of the TMS coil placed tangentially on the skull in relation to the neuronal layer and its main fiber system, i.e. it will probably make a difference whether the target region lays on the outer convexity of a gyrus or the part descending into the sulcus. This assumption may be applicable to both cortical and subcortical regions. To date, however, it is not feasible to target TMS to certain neuronal populations or cortical layers or even to differentially stimulate grey matter and white matter tracts. That means that stimulation effects in the network represent sum or net effects of neuronal and axonal stimulation.

For the motor cortex, a threshold for stimulation effects has been defined, i.e. the resting or active motor threshold which varies interindividually and is also applied to define stimulation intensity at nonmotor sites. Similar thresholds can also be assumed for other cortex regions, e.g. the threshold for eliciting phosphenes over the visual cortex. However, these are not equal to the motor thresholds and not necessarily correlated with them. These threshold measures are specific to neurophysiological phenomena and sum thresholds of component thresholds representing neuronal subpopulations and intracortical, as well

as cortico-subcortical networks. As the intensity is increased, a larger volume of the neuronal network is activated above a given threshold and further neuronal populations in the same volume are additionally depolarized. This may be the background for recruitment curves at primary motor sites and intensity-efficacy relationships observed with prefrontal TMS using clinical, neurophysiological or neuroimaging paradigms [19–21].

Similar considerations are important when we turn to deep TMS approaches. However, the situation is even more complex, as the target regions show greater variance in terms of cytoarchitecture compared to neocortical areas and regions or nuclei with fundamentally distinct functions are located in close vicinity to each other. There are particularly interesting deeper brain regions for therapeutic interventions: the anterior cingulate cortex may be a putative target region for the treatment of major depression and schizophrenia, the hippocampus for the treatment of schizophrenia, depressive disorders and dementia, the amygdala for anxiety disorders and depression, the orbital frontal cortex for obsessive-compulsive disorder, the nucleus accumbens/ventral striatum for addiction, obsessive-compulsive disorder and depression, and the basal ganglia for movement disorders. Actually, each specific application may require a different TMS coil design which has to be based on physical calculations and anatomical considerations tested in clinical practice. However, it is important to emphasize the basic principles of specific coil designs which are described in this overview.

Basic Principles of Transcranial Magnetic Stimulation

The Basic TMS Circuit

The TMS circuit consists of a high-voltage power supply that charges a capacitor or a bank of capacitors, which are then rapidly discharged via an electronic switch into the TMS coil to create the briefly changing magnetic field pulse. A typical circuit is shown in figure 1, where low-voltage AC is transformed into high-voltage DC, which charges the capacitor. A crucial component is the thyristor switch, which has to traverse very high current at a very short time of 50–250 μ s. The cycle time depends on the capacitance (typically 10–250 μ F) and on the coil inductance (typically 10–30 μ H). Accepted ranges of peak currents and voltages may be 2,000–10,000 A (typically 5,000 A) and 500–3,000 V (typically 1,500 V), respectively.

The first TMS stimulators produced a monophasic pulse of electric current. Currently, it is accepted to use stimulators with biphasic pulses, for two reasons: (a) a considerable part of the energy returns to the capacitor at the end of the cycle, thus shortening the time for recharging and enabling to save

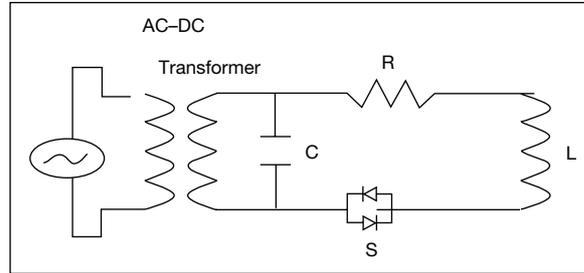


Fig. 1. A schematic TMS circuit, including a DC-AC transformer and amplifier, a capacitor C, high current switch S, resistor R and stimulating coil L.

energy; (b) it was found that the threshold for neuronal activation is generally lower with biphasic compared to monophasic pulses.

During the discharge cycle, the TMS circuit behaves like an RCL circuit, where R, C and L are the total values of the resistance, capacitance and inductance, respectively, in the circuit. The duration τ of one pulse cycle is approximately:

$$\tau = 2\pi\sqrt{LC} \quad (1)$$

The importance of the pulse duration for neuronal activation will be discussed later in this chapter.

Physical and Spatial Factors Affecting Neuronal Activation by TMS

In principle, two related parameters may be relevant for neuronal activation: the electric field strength, and the spatial derivative of the electric field. While the activation of peripheral nerves depends mainly on the derivative of the electric field along the nerve fiber [18], where we deal with neuronal tissue having relatively short axons with bends and branches, such as the brain, it was predicted theoretically [22, 23], and clearly demonstrated experimentally [24–26], that the absolute magnitude of the electric field is the biologically relevant parameter for neuronal stimulation. The electric field is proportional to the rate of change of the current (di/dt) in the stimulating coil. The brief strong current generates a time-varying magnetic field B. An electric field E_A is generated in every point in space with the direction perpendicular to the magnetic field, and the amplitude proportional to the time rate of change of the vector potential $A(r)$.

Since brain tissue has conducting properties, while the air and skull are almost complete insulators, the vector potential will induce accumulation of electric charge at the brain surface. This charge is another source for an electric

field, E_ϕ , in addition to E_A . The influence of the electrostatic field E_ϕ is in general to oppose the induced field E_A and consequently to reduce the total field E . The amount of surface charge produced and hence the magnitude of E_ϕ depends strongly on the coil configuration and orientation. This issue will be elaborated in the following section.

As shown by Heller and Van Hulsteyn [27], the three-dimensional maximum of the electric field intensity will always be located at the brain surface, for any configuration or superposition of TMS coils. It is possible, however, to increase considerably the penetration depth and the percentage of electric field intensity in deep brain regions, relative to the maximal field at the cortex. The next section will outline the construction principles for efficient deep brain stimulation, and will demonstrate several examples of TMS coils designed to accomplish this goal.

Deep Transcranial Magnetic Stimulation Coils

Design Principles

As mentioned above, neuronal stimulation occurs when the electric field magnitude reaches a certain threshold. This threshold, though, depends on the orientation of the induced field. Physiological studies indicate that optimal activation occurs when the field is oriented in the same direction as the nerve fiber [15, 24, 28–33]. 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 neuronal structures or axons under consideration.

The construction of deep TMS coils should meet several goals:

- (a) high enough electric field intensity in the desired deep brain region that will surpass the threshold for neuronal activation;
- (b) high percentage of electric field in the desired deep brain region relative to the maximal intensity in the cortex;
- (c) minimal adverse side effects such as pain and activation of facial muscles.

These motivations have led to the development of the Hsed coil (H-coil), a new design of TMS coils, enabling effective stimulation of deep brain regions without inducing an unbearable field in cortical regions [34]. The ability of the H-coil to stimulate deep brain regions was demonstrated using mathematical simulations as well as measurements performed in a phantom brain model [34]. The efficacy of the H-coil in activating distant brain structures was demonstrated clinically in a recent study, where the motor cortex was activated at a distance of 5–6 cm in healthy volunteers, compared to 1.5 cm with a standard figure-of-eight coil [35].

The geometrical features of each specific design are mainly dependent on two goals: (a) the location and size of the deep brain region or regions intended to be activated; (b) the preferred direction or directions of stimulation.

The design of a specific coil is dictated by these goals. Nevertheless, all deep TMS coils have to share the following important features.

(1) *Base complementary to the human head.* The part of the coil close to the head (the base) must be optimally complementary to the human skull at the desired region. In some coils, the base may be flexible and able to receive the shape of an individual patient, and in other coils it may be more robust, i.e. arcuated in a shape that fits the average human skull at the desired region. In this last case, there may be a few similar models designed to fit smaller and larger heads. This feature guarantees that all the wires in the base will be tangential to the head. This configuration maximizes both the intensity and the penetration depth of the electric field induced by the base in the brain.

(2) *Proper orientation of stimulating coil elements.* Coils must be oriented such that they will produce a considerable field in a direction tangential to the surface, which should also be the preferable direction to activate the neuronal structures under consideration.

(3) *Summation of electric impulses.* The induced electric field in the desired deep brain regions is obtained by optimal summation of electric fields, induced by several coil elements with common direction, in different locations around the skull. The principle of summation may be applied in several manners.

(a) *One-point spatial summation.* In this kind of summation, coil elements, leading current in the desired direction, are placed in various locations around the head, in such a configuration to create high electric field intensity in a specific deep brain region, which at the same time is a high percentage of the maximal electric field at the brain cortex.

(b) *Morphological line spatial summation.* The goal of this summation is to induce an electric field at several points along a certain neuronal structure. This line should not be straight and may have a complex bent path. The application of diffusion tensor imaging in MRI for fiber tracking is an evolving field, which may significantly improve the efficacy of TMS treatment. If, for example, we know the path of a certain axonal bundle, a coil shall be designed in a configuration that will produce a significant electric field at several points along the bundle. This configuration may enable the induction of an action potential in this bundle, while minimizing the activation of other brain regions. For example, the TMS coil may be activated in an intensity that will induce a subthreshold electric field at most brain regions, which will not cause an action potential, while the induction of a subthreshold field along the desired path may produce an action potential in this bundle, thus increasing the specificity of the TMS treatment.

(4) *Minimization of nontangential components.* Coil construction is meant to minimize wire elements leading current components which are nontangential to the skull. Electric field intensity in the tissue to be stimulated and the rate of decrease of electric field as a function of the distance from the coil depend on the orientation of the coil elements relative to the tissue surface. It has been shown [8–10, 34] that coil elements which are nontangential to the surface induce accumulation of surface charge, which leads to the cancellation of the perpendicular component of the induced field at all points within the tissue, and usually to the reduction of the electric field in all other directions. At each specific point, the produced electric field is affected by the lengths of the nontangential components, and their distances from this point. Thus, the length of coil elements which are not tangential to the brain tissue surface should be minimized. Furthermore, the nontangential coil elements should be as small as possible and placed as far as possible from the deep region to be activated.

(5) *Remote location of return paths.* The wires leading currents in a direction opposite to the preferred direction (the return paths) should be located far from the base and the desired brain region. This enables a higher absolute electric field in the desired brain region. In some cases, the return paths may be in the air, i.e. far from the head. In other cases, part of the return paths may be adjacent to a different region in the head which is distant from the desired brain region.

(6) *Shielding.* Feature 5 enables the possibility of screening. Since the return paths are far from the main base, it is possible to screen all or part of their field by inserting a shield around them or between them and the base. The shield is comprised of a material with high magnetic permeability, capable of inhibiting or diverting a magnetic field, such as mu-metal, iron or steel core. Alternatively, the shield is comprised of a metal with high conductivity which can cause electric currents or charge accumulation that may oppose the effect produced by the return portions.

Specific deep TMS coils for stimulating different deep brain regions are described below.

Examples of Deep TMS Coils

The biological efficacy of the H-coil was tested [35], using the right abductor pollicis brevis (APB) muscle motor threshold as a measure of a biological effect. The rate of decrease of the electric field as a function of the 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 a standard figure-of-eight coil. A sketch of the H-coil version used is shown in figure 2.

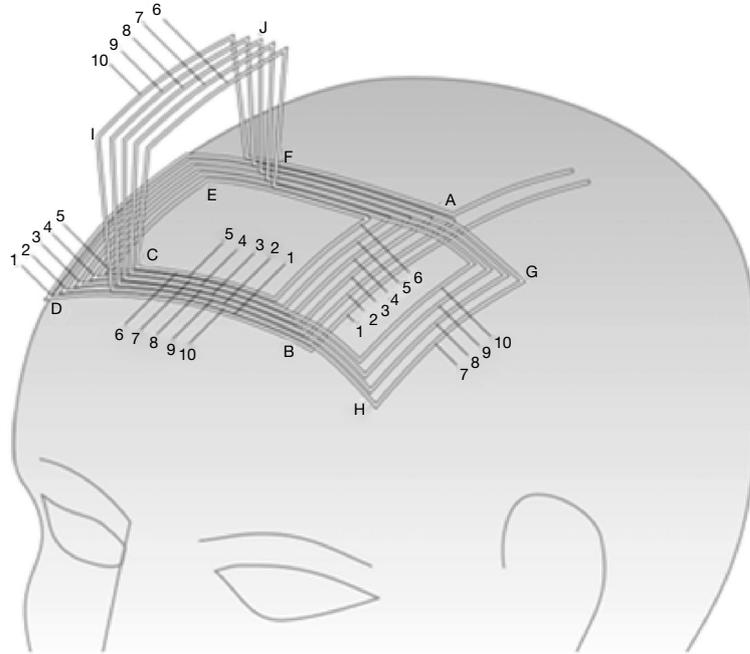


Fig. 2. Sketch of the H-coil version used for activation of the APB, placed on a human head.

The percentage of stimulator output required for APB activation by the H-coil and by a figure-of-eight coil is plotted in figure 3 as a function of the 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-of-eight coil. When using the maximal stimulation power output, the figure-of-eight coil can be effective (reach the 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. Thus, 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-of-eight coil.

The following example is an H-coil designed for stimulation of deep prefrontal regions [unpubl. data]. Medial prefrontal and orbitofrontal cortices and their connections to deeper brain sites are known to be associated with reward processes and motivation [36–42].

The H-coil version used, termed the H1 coil, was designed for effective activation of cortical and subcortical prefrontal and orbitofrontal neuronal

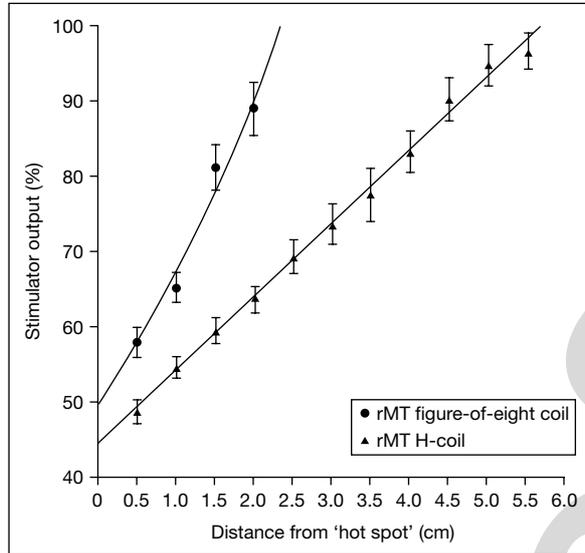


Fig. 3. Intensity needed for APB stimulation at different heights above the scalp. Resting motor threshold (rMT) of the APB was measured at different distances above the 'hot spot' when using either the H-coil or the figure-of-eight coil. The percentage of stimulator power needed to reach the resting motor threshold versus the distance of the coil from the 'hot spot' on the skull is plotted. The points represent means and SDs of 6 healthy volunteers.

structures, with a preference for the left hemisphere. A sketch of the H1 coil version is shown in figure 4.

The electric field distribution produced by the H1 coil was measured in a brain phantom filled with 0.9% weight/volume saline, and compared to a standard Magstim figure-of-eight coil with an internal loop diameter of 7 cm, and a Magstim double-cone coil. The double-cone coil is considered to be able to stimulate deeper brain regions compared to other coils [11–13].

The penetration depth of the coils was tested by measuring the electric field along the up-down line beneath the center of the most effective part of the coil, at 100% output of the Magstim Rapid stimulator. In H1, the most effective part was under strip 8 (lower third of A-I 8 segment in fig. 4), where the probe is oriented in an anterior-posterior direction. In the double-cone coil and the figure-of-eight coil, the most effective part was the junction at the coil center, where the probe is oriented in an anterior-posterior direction. Plots of the total electric field as a function of distance are shown in figure 5.

Figure 6 shows the electric field as a function of distance, relative to the field at a distance of 1 cm, for the three coils.

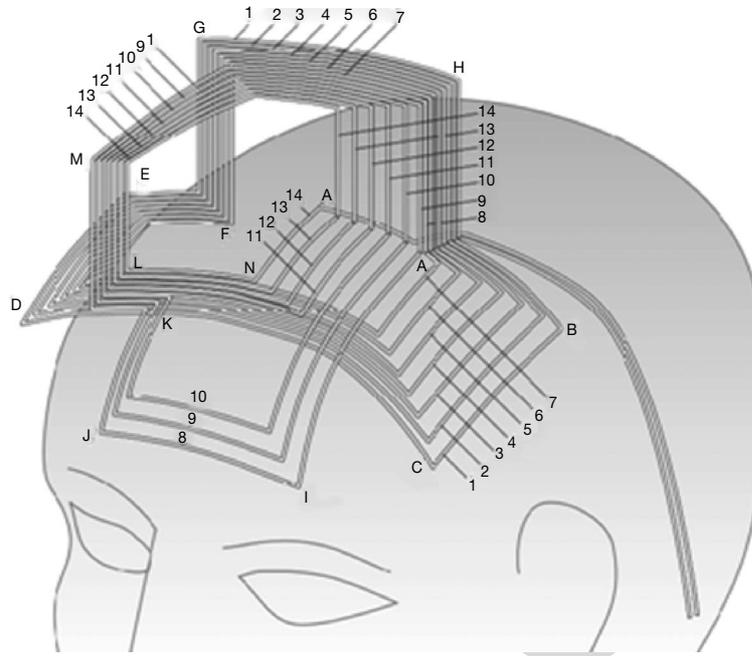


Fig. 4. Sketch of the H1 coil used for effective activation of prefrontal brain regions, placed on a human head.

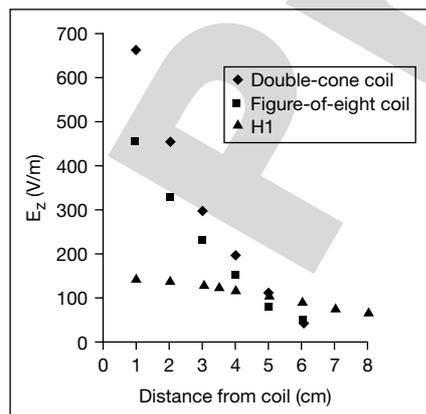


Fig. 5. Phantom measurements of the electric field along an anterior-posterior axis, plotted as a function of distance, for the H1 coil, the double-cone coil, and the figure-of-eight coil.

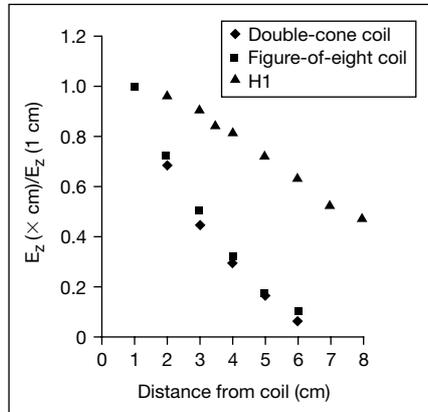


Fig. 6. Electric field relative to the field 1 cm from the coil, as a function of distance, for the H1 coil, the double-cone coil and the figure-of-eight coil, according to the phantom brain measurements.

It can be seen that the total electric field induced by the double-cone coil, and by the figure-of-eight coil, using the maximal output of the stimulator, is markedly greater than the field produced by the H1 coil at a short distances of 1–2 cm. Yet, at distances of above 5 cm, the field of the H1 coil becomes greater, due to its much slower rate of decay. In figure 6, it can be seen that the percentage of depth for the H1 coil is greater than for the two other coils already at a 2-cm distance, and this advantage becomes more prominent with increasing distance. The field produced by the H1 coil at a 6-cm depth is about 63% of the field 1 cm from the coil, while the fields of the double-cone coil and the figure-of-eight coil attenuate to 8–10% at this distance.

In summary, it was demonstrated that the H-coils enable to achieve effective stimulation of deep neuronal regions without inducing an unbearable field in cortical regions. Yet, using H-coils with available TMS stimulators enables effective activation of deep brain regions, but not focal activation. In order to obtain a focused stimulation of deep brain regions, and to considerably enhance the stimulation efficiency, novel TMS systems are required, which account for the temporal properties of neuronal structures. This is the subject of the next section.

Novel Deep Transcranial Magnetic Stimulation Systems Based on the Time Summation Principle

Temporal Factors Affecting Neuronal Activation by TMS

In addition to the electric field strength, the neuronal response also strongly depends on the duration of the pulse.

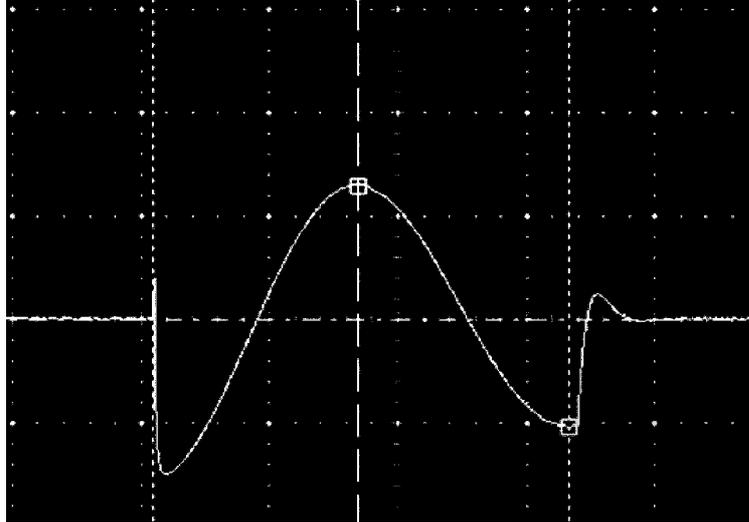


Fig. 7. The induced electric field of a figure-of-eight coil versus time over a TMS pulse cycle. The time scale is 100 μs .

Figure 7 demonstrates the electric field pulse produced by a figure-of-eight coil, as measured by a two-wire probe in a brain phantom filled with saline solution at a physiologic concentration. In rTMS, several such pulses are administered in a train of between 0.2 and 100 Hz, and typically between 1 and 20 Hz.

The longer the pulse duration, the smaller the electric field required to reach neuronal threshold E_{thr} . The dependence of E_{thr} on pulse duration is given by a strength-duration curve [43] of the form:

$$E_{\text{thr}} = b(1 + c/\tau) \quad (2)$$

The biological parameters determining neural response are the threshold at infinite duration, termed the rheobase (b , measured in V/m), and the duration at which the threshold is twice the rheobase, termed the chronaxie (c , in μs), which is related to the time constant of the neuronal membrane. The chronaxie and rheobase depend on many biological and experimental factors, such as whether the nerves are myelinated or not (hence peripheral and cortical parameters should be different), the pulse shape (i.e. biphasic or monophasic), or train frequency in rTMS, which in general reduces the threshold for stimulation.

In figure 8, a strength-duration curve is shown reflecting the average of 4 subjects, using eight different coils with inductance L of between 6 and 148 μH .

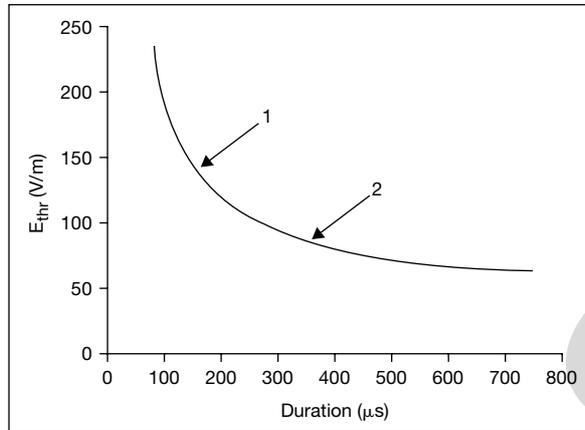


Fig. 8. A strength-duration curve obtained for the hand motor cortex of 4 subjects, using variable coil inductance. Points 1 and 2 represent results obtained with coils having an inductance of 13 and 70 μH , respectively.

As can be seen from equation 1, the duration of a TMS pulse can be extended in two ways: by increasing the capacitance C , or by increasing the coil inductance L . In regular available stimulators, C is constant. Increasing L is not desired, since it leads to increased power and energy consumption.

Figure 9 shows pulses produced by TMS coils having inductances of 13 and 70 μH . The amplitudes represent the threshold electric field according to points 1 and 2 in the strength-duration curve shown in figure 8. The plots are for resistance and capacitance of $R = 0.1 \Omega$ and $C = 165 \mu\text{F}$, respectively. It can be seen that when the pulse duration is longer, the required threshold electric field is smaller.

When we want to produce focused activation of deep neuronal structures in the brain, regular TMS stimulators have significant limitations. In available stimulators, the capacitor (or bank of capacitors) is discharged through a single switch to a single coil, hence the current flows simultaneously through all coil elements, and the electric field is produced simultaneously in all brain regions. Thus, the electric field induced in cortical brain regions close to coil elements will be in general larger than the field induced in deeper brain regions. In the following part, we describe the time summation principle and suited TMS system, which may enable to overcome this difficulty.

Principles of Time Summation Multichannel TMS Systems

The principle of time summation is that various TMS coils may be stimulated consecutively and not simultaneously. As shown in figure 8, the neuronal

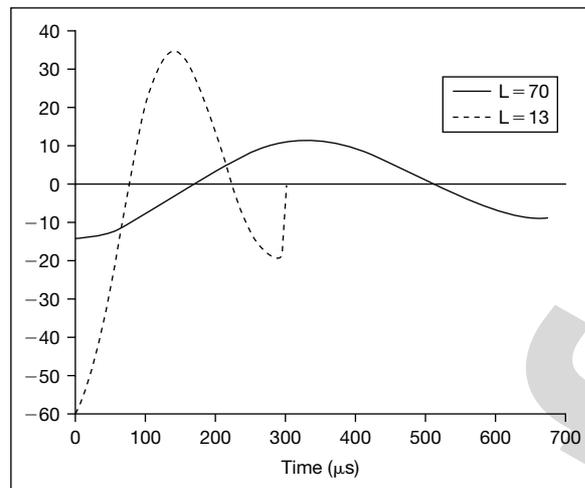


Fig. 9. The electric field pulse produced by two TMS coils with inductances of 13 and 70 μH , as a function of time.

activation threshold depends on both electric field intensity and the stimulation duration. When we want to stimulate a specific deep brain region, various coils, or alternatively various coil elements connected in parallel, may be scattered around the desired region or path, so that passing a current in each coil will produce a significant field at the desired deep brain region. Each coil may be connected to a separate TMS channel. In such a case, the coils may be activated consecutively, so that at each time period only a certain coil or a group of coils are activated. This way, a significant electric field will be induced in the desired deep brain region at all time periods, while in more cortical regions a significant field will be induced mainly at certain periods, when proximate coils or coil elements are activated. This will enable stimulation of the deep brain structure while minimizing stimulation of other brain regions, and specifically of cortical regions.

The novel TMS systems require several capacitors, which are discharged in different channels through different switches into different TMS coils or different elements of coil connected in parallel. A control unit should control the times of charging and discharging of the different capacitors, and the delays between operation times of sequential coils. Various coils or coil elements may be operated sequentially, with delays of between 0 and 1 ms. The relevant time scale for neuronal response is usually on the order of 10–100 μs . In each operation, one TMS cycle is induced through a certain coil or several coils. The

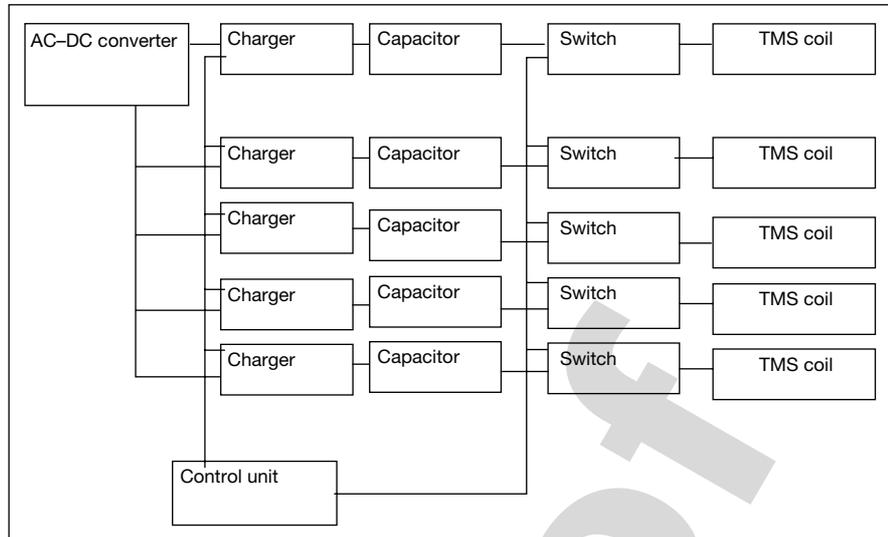


Fig. 10. A schematic diagram of a multichannel TMS system, having 5 channels.

number of different coils or coil elements may be different in different applications. In some cases, the delays between consecutive operations of coils will be the same, while in other cases they may be different between different operations and different coils.

A schematic example of a block diagram of a multichannel TMS system that enables to apply the time summation principle is shown in figure 10.

In the example shown in figure 10, there are five channels. The system may include an AC–DC converter, which converts the AC voltage of the electricity mains to a DC voltage. In each channel, there may be a charging circuit, one or more capacitors, and a high current fast switch through which the capacitor/capacitors is/are discharged.

The operator will be able to control the delays between the operation times of the different coils, the number of different channels and coils operated consecutively, the number of times each coil will be activated and the timing of each activation, the polarity of the current in each coil, the frequency of operation (i.e. number of pulses in seconds), the train duration, the number of trains and intertrain intervals, and the power output of operation of each coil. The ability to control the delays between operations of the different coils and the current polarity in each coil enables various kinds of time summation. Several examples are given below.

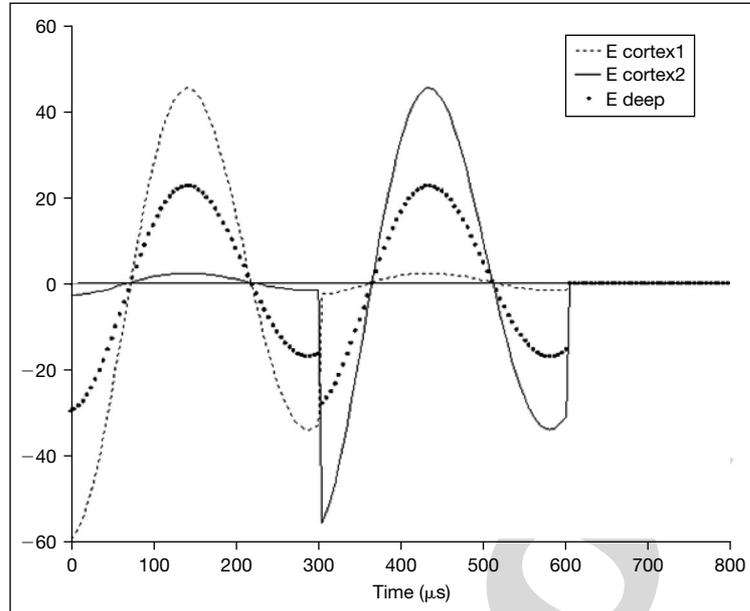


Fig. 11. An example of time summation where the time delay between consecutive pulses is a full cycle. Shown are the electric field pulses induced in cortical regions close to each coil (continuous and dashed curves) and in a deep brain region (dotted curve).

Examples of Time Summation

Figure 11 shows the electric field pulses induced in a deep brain region and in two cortical regions, where the pulse of the coil close to the second cortical region lags the pulse of the coil close to the first cortical region by a full cycle. In each coil, one pulse cycle is induced, and the switch is disconnected at the end of a cycle when the current is zero. In this and in the following examples, the field intensity in the deep brain region is 50% of the intensity induced in the cortical region close to the equivalent coil (this percentage is realistic with the H-coils), while the field intensity in one of the cortical regions during operation of the coil close to the second cortical region is 5%. Hence in the deep brain region a significant electric field is induced during all the consecutive pulses, while in each of the cortical regions a significant field is induced only during one cycle.

Obviously, the same principles may be applied with more than two coils, and/or with several or all of the coils operated more than once.

Figure 12 shows the electric field pulses induced in a deep brain region and in three cortical regions, where the delay between two consecutive pulses is half

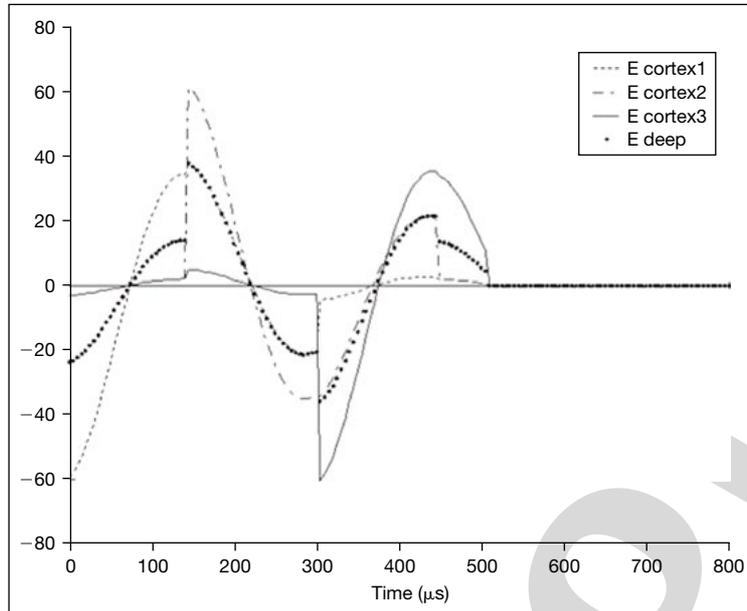


Fig. 12. An example of time summation where the time delay between consecutive pulses is half a cycle, and the current polarity in the second pulse is opposite to the polarity in the first and third pulses. Shown are the electric field pulses induced in cortical regions close to each coil (dashed, dot-dashed and continuous curves) and in a deep brain region (dotted curve).

a cycle, and the current polarity in the second pulse is opposite to the polarity in the first and third pulses. In each coil, one pulse cycle is induced, and the switch is disconnected at the end of a cycle when the current is zero. In this example, there is an extension of the duration at which the deep brain region is exposed to a significant field, and in addition there is an increase in intensity after each half cycle. Note that the absolute value of the maximum at the beginning of each pulse is higher than the next maxima due to the decay factor $\alpha = R/2L$, hence at the beginning of the second pulse the relation between the field in the deep brain region and the field in the first cortical region will be higher with higher circuit resistance R , and with lower coil inductance L .

Figure 13 shows the electric field pulses induced in a deep brain region and in three cortical regions, where the current polarity in the second and third pulses is opposite to the polarity in the first pulse. The delay between the first and second pulses is close to $3/4$ of a cycle, and the delay between the second and third pulses is about $1/8$ of a cycle. In each coil, one pulse cycle is induced,

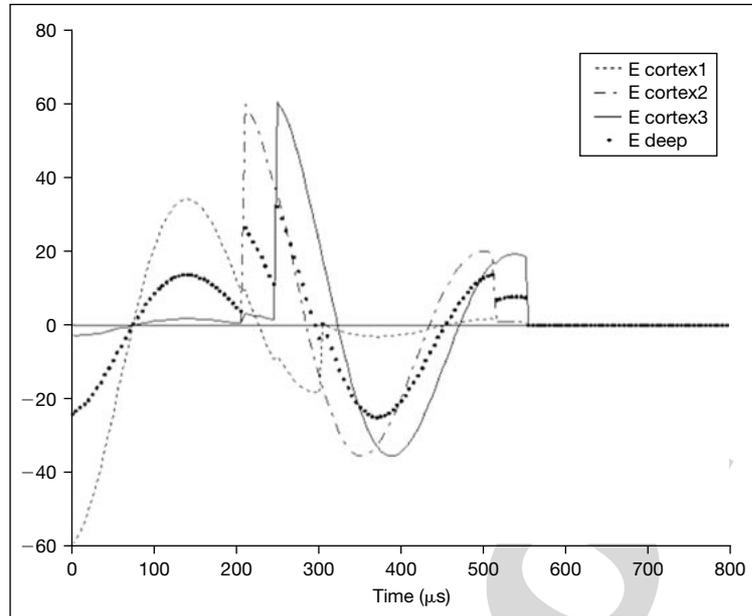


Fig. 13. An example of time summation where the current polarity in the second and third pulses is opposite to the polarity in the first pulses, and there is an extension of the duration of the positive half cycle in the deep brain region, and an increase in the intensity. Shown are the electric field pulses induced in cortical regions close to each coil (dashed, dot-dashed and continuous curves) and in a deep brain region (dotted curve).

and the switch is disconnected at the end of a cycle when the current is zero. In this example, there is an extension of the duration of the positive half cycle in the deep brain region, and an increase in intensity. Obviously, the same principles may be applied with more than three coils, and/or with several or all of the coils operated more than once. In different applications, more than one pulse may be induced in part or all of the coils. This way, the time duration at which the deep brain region experiences a significant induced field may be extended. Thus, the stimulator power output required to activate neuronal structures in this deep brain region may be lowered, and the ability to activate the deep brain region without activating cortical regions – or with minimally activating cortical regions – may be improved.

The efficiency and focality of stimulation of deep brain regions using the time summation principle with a multichannel TMS system depend on the penetration depth of the electric field induced by the TMS coils of the various channels. Where we have better penetration depth, it is easier to obtain neuronal

stimulation in the desired deep brain region without activating superficial regions. The H-coils are optimized to achieve both maximal absolute field strength at depth, and a high percentage of field relative to the cortex. Hence the usage of coils designed according to the construction principles of the H-coils, as the stimulating coils of the various channels, is predicted to be advantageous in terms of efficiency, focality, flexibility, and energy and power consumption.

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Abraham Zangen, PhD
The Weizmann Institute of Science, Department of Neurobiology
Rehovot, 76100 (Israel)
Tel. +972 8 934 4415, Fax +972 8 934 4131, E-Mail a.zangen@weizmann.ac.il