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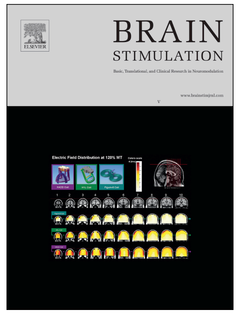

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Rotational field TMS: Comparison with conventional TMS based on motor evoked potentials and thresholds in the hand and leg motor cortices

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Abstract

Background: Transcranial magnetic stimulation (TMS) is a rapidly expanding technology utilized in research and neuropsychiatric treatments. Yet, conventional TMS configurations affect primarily neurons that are aligned parallel to the induced electric field by a fixed coil, making the activation orientation-specific. A novel method termed rotational field TMS (rfTMS), where two orthogonal coils are operated with a 90° phase shift, produces rotation of the electric field vector over almost a complete cycle, and may stimulate larger portion of the neuronal population within a given brain area.

Objective: To compare the physiological effects of rfTMS and conventional unidirectional TMS (udTMS) in the motor cortex.

Methods: Hand and leg resting motor thresholds (rMT), and motor evoked potential (MEP) amplitudes and latencies (at 120% of rMT), were measured using a dual-coil array based on the H7-coil, in 8 healthy volunteers following stimulation at different orientations of either udTMS or rfTMS.

Results: For both target areas rfTMS produced significantly lower rMTs and much higher MEPs than those induced by udTMS, for comparable induced electric field amplitude. Both hand and leg rMTs were orientation-dependent.

Conclusions: rfTMS induces stronger physiologic effects in targeted brain regions at significantly lower intensities. Importantly, given the activation of a much larger population of neurons within a certain brain area, repeated application of rfTMS may induce different neuroplastic effects in neural networks, opening novel research and clinical opportunities.

Keywords: TMS, Rotational field, Unidirectional, Motor cortex, MEP, Motor threshold

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique where a transient current pulse is passed in a coil placed on the scalp, inducing electric field that can activate neurons in the underlying brain tissue (1). The ability to non-invasively and safely modulate neural activity with a high degree of temporal resolution has led to unique and important developments in various fields of diagnostics (2) and neuroscience (3). Moreover, the ability of repetitive TMS (rTMS) to induce long-term neuroplastic changes in the excitability and connectivity of relevant brain circuits bears great promise as a therapeutic intervention for various neuropsychiatric indications (3, 4). rTMS is now extensively used in psychiatric treatments following large double-blind placebo-controlled (DBPC) multicenter trials (5-8) that led to US Food and Drug Administration (FDA) clearance for the treatment of major depressive disorder (MDD) with figure-8 or H1 TMS coils and for the treatment of obsessive-compulsive disorder (OCD) with the H7 TMS coil. The figure-of-8 and the H-coils differ with regard to the generated electric field, such that the figure-of-8 induces a focal and superficial electric field underneath the coil, while the H-coils allow deeper and broader penetration of electromagnetic stimulation into the brain (9).

For any TMS coil, the neural response is influenced dramatically by the coil current polarity and orientation relative to the brain tissue morphology (10-12). In the cortex, neural stimulation occurs in general at points where the axon is parallel to the TMS electric field and bends away from it (13-17). Hence, the most likely sites of stimulation are points of bend, branching, axon initial segments or axon terminals in axons parallel to the induced electric field (18). Furthermore, the current polarity along the nerve axis is crucial, as for a certain polarity a membrane depolarization will occur, which above a critical value may lead to neural stimulation. On the other hand, the opposite polarity will lead to membrane hyperpolarization which reduces the chance for stimulation (18). Hence, in conventional unidirectional TMS (udTMS) the effect is limited to mainly structures aligned parallel to the induced electric field, and only a small portion of the neural population in each brain region is activated. Moreover, inter-individual variability in specific brain morphology may significantly affect the induced electric field distribution (19), and this may at least partially explain the great observed variability in excitability modulation magnitude and even direction of effect (20) and the variability in clinical outcomes.

A recent study (21) presented a novel method, termed rotational field TMS (rfTMS), where two orthogonal coils are operated with a 90° phase shift between them. Hence, the generated electric field vector of rfTMS is circularly polarized and rotates over an almost complete cycle and thus affects neural structures in various orientations. In the current study we utilized a coil array based on the H7 coil, and tested rfTMS effects on human hand and leg resting motor threshold (rMT), as well as supra-threshold motor evoked potential (MEP), in comparison to udTMS in various orientations.

Materials and methods

Participants

Eight healthy volunteers (1 female; mean age 39.3 ± 2.4 years) were enrolled in the study. Participants were screened for safety contraindications for TMS (22). The experimental procedures were approved by and in accordance with the local Helsinki ethics committee of Soroka-Ben-Gurion Medical center. All participants gave informed consent prior to the study.

TMS

A novel dual-channel deep TMS system was built (23), with capacitance of 180 µF on both channels, producing biphasic pulses. They were connected to a specially designed coil array that comprises the H7 coil (5) as the lower coil, with main induced field along postero-anterior (P-A) axis, and an upper coil in an orthogonal orientation and a matched inductance of 14 µH (Brainsway, Jerusalem, Israel). A sketch of the coil array over a human head is shown on Fig. 1a, and an image of the array is shown in Fig. 1b.

INSERT FIG. 1

The exact timing and current polarity of the two coils were controlled, as detailed below.

The experiments were done in three settings:

a. **Unidirectional operation:** udTMS was produced by either operating each coil separately, or simultaneously with no phase shift, in all polarity combinations. This led to udTMS in eight orientations 45° apart, with angle 0° defined as the induced current in the brain during the first stroke of the biphasic pulse directed along the anterior-posterior (A-P) axis. Hence, the induced current during the second, larger biphasic pulse stroke, was P-A. Angle 90° was defined as the induced current in the brain during the second stroke of the biphasic pulse is left-right (lateral-medial (L-M) on the left hemisphere).

b. **Rotational field operation:** Operation of the rfTMS coil array where the upper coil is operated with a lag of a quarter of a cycle after the lower coil (Fig. 2a), thus inducing a rotational field. rfTMS was implemented with four polarity states of the two coils in the array, where in each state a different 270° portion of the phase space was spanned by the field vector (Fig. 2b). The polarities were induced such that during the second stroke of the biphasic pulse by the lower and upper coils the induced current in the brain was P-A and L-M (left-right on the left hemisphere) (↑→), A-P and M-L (↓←), P-A and M-L (↑←), or A-P and L-M (↓→), respectively (Fig. S1).

INSERT FIG. 2

The order of the udTMS and rfTMS conditions (12 states overall) was randomized so that half of the subjects started with a udTMS measure while the other half started with a rfTMS measure, the first angel was selected so as to be different from the one selected in the previous subject, and subsequent angels were clockwise in half of subjects and anti-clockwise in the other half.

c. **Two coils in parallel operation:** Operation of the coil array with the two coils having the same orientation, with induced field in the brain during the second stroke of the biphasic pulse in the P-A orientation, where the upper coil is operated with a lag of a quarter of a cycle after the lower coil (Fig. 3). The pulses of the two coils are biphasic, hence, a conventional unidirectional electric field is induced, but with pulse duration of 1.25*(the cycle time of a single coil). This setting was tested in order to see if there is any effect of merely lengthening the pulse duration.

INSERT FIG. 3

EMG measurements

The right hand abductor policis brevis (APB) and right leg tibialis anterior (TA) rMT were measured with electromyography (EMG) (VikingQuest, Carefusion, USA; band-pass filtered 2-10kHz, digitized at 10kHz; surface EMG electrodes Covidien KittyCat, Dublin, Ireland; arranged in belly-tendon arrangement over each muscle) for conditions a and b above. Pulses were administered with intervals of at least 4 seconds. Threshold was defined as the stimulator intensity required to elicit MEP of at least 50 µV in 5 out of 10 trials. The subjects were asked to maintain their muscles at rest throughout the procedure. For both the APB and the TA muscles, the coil array was positioned with the lower H7 coil along A-P axis and the upper coil along lateral-medial (L-M) axis, and the optimal spot on the scalp for motor stimulation with the H7 coil was localized. Positioning was carried out using a cap to which was attached a 5-mm resolution grid. A transparent navigation strip on the coils array was used to maneuver to the correct location on the grid. This enabled location of the optimal spot for motor stimulation, and maintenance of stable position and orientation throughout the procedure. After hot spot localization, the coil array was attached to the head with a series of straps, and rMT was determined for all orientations by changing current polarities in the two coils, without moving the array. In all the rfTMS and udTMS conditions, the ratio between the intensities of the two coils was kept constant so that they induced identical electric field at the relevant motor cortex. Simultaneous operation of the two coils with certain polarities resulted in udTMS along an oblique axis (at angles 45°, 135°, 225° or 315°). In these conditions, an electric field is induced along the oblique axis with an amplitude of √2*the amplitude of one of the coils. Operation with a lag of ¼ cycle of the upper coil after the lower coil led to rfTMS. Since the ratio between the intensities of the two coils was kept constant so that they induced identical electric field at the relevant motor cortex, the electric field amplitude was constant during the rotation, and identical electric field amplitude was induced at each direction. During the process of rMT determination in all the different udTMS and rfTMS combinations, the ratios of intensities of the upper and lower coils were kept constant so that the two coils induced the same electric field at a depth of

1.5 cm for the hand rMT measurements, and a depth of 2.5 cm for the leg rMT measurements (23, 25), as measured in a phantom head model (25). For udTMS at angles of 45°, 135°, 225° and 315° the intensities of the two coils were reduced while maintaining the same ratio, until the motor threshold was reached. Thus, it was guaranteed that the two coils induced the same electric field at the relevant motor cortex. For angles of 0°, 90°, 180° and 270° the intensity of one coil was gradually reduced until rMT was determined. In each condition, the rMT was calculated relative to the condition of the lower coil at angle 0°, based on the ratio of the total electric field induced (at rMT) at the relevant motor cortex. In addition to rMT determination, we measured for each condition the amplitude and latency of MEP evoked at a stimulator output of 120% of the rMT with the single H7 coil oriented A-P (angle 0°). For each rfTMS and udTMS condition, the intensities were matched to induce an electric field of 120% of the field induced by the lower H7 coil oriented A-P, at threshold. MEP areas were averaged over 5 trials for each case, with inter-trial intervals of 4 seconds. This was done for both the hand and the leg. All results of rMT and MEP are given as % of the values of the lower H7 coil oriented A-P.

Measurement of electric field

The induced electric field amplitudes of the lower and upper coil, and of operation in setting c above, where the coils are parallel – rather than orthogonal - and the upper coil is operated with a lag of a ¼ of a cycle after the lower coil, were measured as described previously (26), and the induced changes in neural trans-membrane potential V_m and energy consumption W_T were calculated (see Supplementary material for details), and compared to those of rfTMS(↑→). The results at the depths of the hand (1.5 cm) and leg (2.5 cm) motor cortex were combined with measurements of hand APB and leg TA rMTs in the four states.

Statistical analysis

Comparisons were done with repeated measures ANOVA with condition (rfTMS vs udTMS) as a factor. Post-hoc tests were carried out using Tukey's test. Since in each rfTMS polarity state a different 270° portion of the phase space is spanned by the field vector, while for a "perfect" rfTMS the whole 360° of the phase space would be spanned, in cases where repeated measures ANOVA found significant effect, paired comparisons were made between the condition of rfTMS and the unidirectional condition that led to the lowert rMTs or highest MEPs. Paired comparisons were done with paired t-test where normality test was passed, and with Wilcoxon test in cases where the normality test failed. Normality tests were done with Kolmogorov–Smirnov (K-S) test. Mean values are quoted together with standard errors (±SE).

Results

rfTMS applied in the present study was safe and did not induce seizures. Four of the subjects reported differing degrees of local but tolerable pain when applied at 120% of the leg motor threshold. The pain has quickly relieved following termination of stimulation.

Hand and leg rMTs were determined in eight subjects. Hand rMT with rfTMS was significantly lower than any udTMS orientation (Fig. 4). A repeated measures ANOVA showed a significant condition effect ($F(1,12)=14.96$, $p<0.0001$), and a comparison between the best rfTMS (↑→) and udTMS (45°) conditions showed significant advantage to rfTMS ($p=0.0014$, paired t-test). There was a significant difference in rMT among unidirectional orientations ($F(1,8)=5.349$, $p<0.0001$), with an angle of 45° to P-A axis yielding the lowest rMT.

INSERT FIG. 4

Leg rMT with rfTMS was significantly lower than any udTMS orientation (Fig. 5). A repeated measures ANOVA showed a significant condition effect ($F(1,12)=44.92$, $p<0.0001$), and a comparison between the best rfTMS (↑←) and udTMS (315°) conditions showed significant advantage to rfTMS ($p<0.0001$, paired t-test). There was a significant difference in rMT among unidirectional orientations ($F(1,8)=2.639$, $p=0.0214$), yet Tukey post-test revealed no significant differences between angles.

INSERT FIG. 5

Hand APB and leg TA rMTs using the lower coil, upper coil, the two coils in parallel (rather than orthogonal) and where the upper coil is operated with a lag of a ¼ of a cycle after the lower coil, and rfTMS (↑→) were determined in two subjects. The results were combined with results of electric field measurements in a phantom head model for these three states. The stimulator power output, electric field, calculated change in trans-membrane potential V_m and energy consumption W_T values are shown in Table S1. As can be seen, all the results are compatible and indicate that for both the hand and leg rMT, threshold for each coil alone or for both coils in parallel occurs with comparable V_m values, but for rfTMS the threshold occurs at much lower values.

Comparison of the results of the four rfTMS polarity states found significant differences for hand rMT ($F(1,4)=15.95$, $p<0.0001$), with the lowest rMT obtained for state ↑→, where the field vector covers also the angle of 45° to the P-A axis (Fig. S1a). In contrast, a marginally significant difference was found for leg rMT ($F(1,4)=3.12$, $p=0.0478$), and Tukey post-test revealed no significant differences between groups.

Comparisons of MEPs

Measured hand supra-threshold MEPs were significantly higher with rfTMS (Fig.6). A repeated measures ANOVA showed a significant condition effect ($F(1,12)=16.14$, $p<0.0001$), and a comparison between the best rfTMS (↑←) and udTMS (45°) conditions showed significant advantage to rfTMS ($p=0.037$). There was a significant difference in MEP among unidirectional orientations ($F(1,8)=5.902$, $p<0.0001$), with an angle of 45° to A-P axis yielding the highest

MEP, and a Tukey post-test revealed significant differences between angle 45° and five other angles (0°, 135°, 180°, 270°, 315°).

INSERT FIG. 6

Measured leg supra-threshold MEPs were significantly higher with rfTMS (Fig.7). A repeated measures ANOVA showed a significant condition effect ($F(1,12)=4.422$, $p<0.0001$), and a comparison between the best rfTMS (↓→) and udTMS (90°) conditions showed a significant advantage to rfTMS ($p=0.0156$, Wilcoxon test). There was no significant difference in MEP among unidirectional orientations ($F(1,8)=0.8942$, $p=0.52$).

INSERT FIG. 7

Comparison of the results of the four rfTMS polarity states found no significant differences for hand MEP ($F(1,4)=0.1871$, $p=0.91$), nor for the leg MEP ($F(1,4)=0.4392$, $p=0.73$).

Comparisons of MEP onset latencies

Mean APB and TA MEP onset latencies are summarized in Table S2. Hand MEP latencies were not significantly different between rfTMS and udTMS ($F(1,12)=1.342$, $p=0.22$), while for the leg, repeated measures ANOVA showed a significant condition effect ($F(1,12)=4.536$, $p<0.0001$). Comparison between the rfTMS condition (↑←) that induced the shortest average latency and all udTMS states showed a significant effect ($F(1,9)=3.911$, $p=0.0013$), and a Tukey post-test revealed a significant difference between the rfTMS state and five of the eight udTMS angles (0°, 45°, 180°, 215° and 270°). Yet, a paired comparison between this rfTMS condition (↑←) and the best udTMS condition (90°) showed no significant difference ($p=0.25$, paired t-test). There was a significant difference in leg MEP latencies among unidirectional orientations ($F(1,8)=2.286$, $p=0.0456$), and a Tukey post-test revealed significant difference between angles 90° (shortest latencies) and 180°. There were no significant differences between the four rfTMS polarity states ($F(1,4)=1.188$, $p=0.34$).

Discussion

Neural activation with TMS is achieved by inducing membrane depolarization in neural structures aligned parallel to the induced electric field (13-17). The hand motor cortex is known to have high sensitivity to orientation, with lowest threshold for motor activation and highest MEPs evoked when the TMS induced field is at 45° to the P-A axis perpendicular to the central sulcus (27, 28). In contrast, the neuronal organization in the leg motor cortex is much more isotropic and has much lower sensitivity to coil orientation (29, 30).

In this study we measured the hand APB and the leg TA rMT as well as the supra-threshold MEPs, for various field orientations, spanning the entire phase space in increments of 45°. The same measurements were carried with the novel rfTMS technique, where the field rotates and spans most of the phase space.

Striking differences were found between rfTMS and udTMS among the measures of corticospinal excitability. rfTMS robustly led to significantly lower rMT and higher supra-threshold MEP values in both the orientation-sensitive hand motor cortex and the much more isotropic leg motor cortex, compared to conventional udTMS for any tested orientation.

For udTMS, in accordance with previous studies (27, 28), we found a significant dependence of the hand APB motor threshold on orientation, with the lowest threshold for rMT and the highest MEP obtained for an angle of 45° to the P-A axis. In contrast, only a weak directional dependence of rMT and no dependence for MEP were found in the leg TA. These results are in line with a study of corticospinal volleys induced by monophasic pulses stimulation of the tibialis motor cortex, which found no dependence of MT on orientation (29), although studies of single motor units (30, 31) did find such a dependence, with induced current in the range of latero-posteriorly to anteriorly seemed to induce lower MTs (30). Richter and colleagues (32) found in the abductor hallucis that optimal orientation for lowest MT was 30° posterior to M-L (analogous to 240° in our definitions). In this study we used biphasic pulses with surface EMG, hence the sensitivity to delicate orientational dependence is limited. Still, our results indicated lower average thresholds for the range of 180° to 315° (posterior, medial-lateral to antero-lateral) compared to lateral-medial directions (see Fig. 5), in accord with Terao et al. (30).

Four rfTMS states, each spanning a different 270° portion of the phase space, yielded significantly different results of APB rMT. The state that did not cover the first quadrant, which includes the preferable 45° angle (state ↓←, see Fig. S1b), had the highest rMT (Fig. 4). The fact that partial rfTMS can span specific portions of the phase space represents an example of utilizing a novel method in brain research. For example, two half-sine pulses with a lag of ¼ of a cycle will cover only one quarter of the 360° phase space, while similar pulses truncated even earlier in their cycle, before the current reaches zero, may lead to rfTMS covering even smaller orientational portions. Such pulses can be produced with approaches such as controllable TMS (33). As another option, operation of two half-sine pulses by the two coils, which have orthogonal orientations or any other relative angle, consecutively with no temporal overlap, will induce field only in these two orientations. Thus, one can map in high resolution the correlativity between neural structures with various orientations within a certain brain region. This functional information may be combined with anatomical DTI information, and increase our understanding of brain circuits, function and architecture. Obviously, for many applications, such as investigations on precisely defined neurophysiological mechanisms, a focal and unidirectional activation is more suited, and the multidirectional activation of rfTMS may not be the optimal strategy when only specific fiber orientations are investigated. Future studies should also investigate rfTMS with common-size figure-8 coils producing focal stimulation. In such cases rfTMS will reduce the need for accurate orientational placement and fixation of the coil, and ease neuronavigation procedures.

Operation of two parallel coils with identical P-A orientation, but with a lag of ¼ a cycle between them, leads to similar energy consumption and dissipation as with a rotational field setup where the coils are orthogonal (Table S1), but without the rotation of the field vector. The combined operation of the two coils therefore merely leads to combination of their induced field along a single orientation, and to a combined pulse with ¼ a cycle longer duration (Fig. 3). The results showed similar trans-membrane potential changes at threshold for this parallel orientation as for operation with each coil separately. Yet rfTMS led to much lower trans-membrane potential changes at threshold (Table S1). This supports the dominant role of the electric field as the main factor that leads to neural stimulation, and that lengthening the pulse duration (or increasing energy) does not yield benefit in neural activation threshold, while rotating the field and recruiting more neural structures with various orientations does.

Interestingly, APB MEP latencies were not significantly different between rfTMS and udTMS, nor were any significant differences found between unidirectional orientations. Monophasic or half-sine pulses with different orientations of the induced electric field in the M1 have been shown to induce different MEP onset latencies, especially during a weak voluntary contraction of the muscle (10, 34-37). Yet, we applied biphasic pulses, which most probably activate different neuronal sites during both phases, thus probably masking orientational dependence of the latencies (38). Moreover, the subjects were instructed to maintain the muscles relaxed, whereas multiple corticospinal excitatory postsynaptic potentials (EPSPs) are required to raise the resting membrane potential of spinal motoneurons above firing threshold, hence onset latencies are longer and more variable (39).

rfTMS yielded significantly shorter latencies for the leg TA compared to most of the udTMS conditions, but was not significantly shorter compared to all orientations. Some studies found shorter latencies for M-L compared to P-A induced currents (40, 41), while in other studies no significant differences were found (29, 31). These results should be seen in the light of the considerable controversy regarding characterization of corticospinal discharges in the leg following electrical and magnetic stimulation (29, 30, 40). Most of these measurements have been based on peristimulus time histograms (PSTH) readings in single motor units. For example, Terao et al. (30) reported that, in single motor units of the TA, some TMS directions tended to evoke more D-waves than others. Our results seem to indicate that the broad recruitment of the rotational field increases the efficiency of D-waves elucidation in the TA.

rfTMS can induce significantly stronger effects in targeted brain regions, enabling achievement of desired physiologic effect at significantly lower intensities, thereby potentially reducing undesired side effects. Given the activation of a much larger population of neurons within a certain brain area, repeated application of rfTMS may induce different and potentially stronger and more robust neuroplastic effects in neural networks, opening novel opportunities for neuroscience and clinical applications. On the other hand, the broader activation of rfTMS may lead to more side effects. Future studies will have to address these questions and investigate the new technique’s potential in various brain disorders.

The concept of rfTMS may be extended to use three or more coils and to induce field rotation in 3-dimensions. Indeed, electric field perpendicular to the brain surface is inefficient in inducing action potentials (26, 42, 43). However, as an example, a third coil may be positioned over the temporal lobe, inducing electric field along a superior-inferior axis. Its operation can be synchronized with an array of two orthogonal coils placed over the frontal or parietal lobe. One of these coils may induce field along an anterior-posterior axis, and the second coil along a lateral-medial axis. In such a setting, each coil induces main field along an axis parallel to the brain surface beneath it, and not perpendicular to the surface. Synchronizing operation of the three coils with intervals of ¼ of a cycle may induce spherically-rotating field in 3-dimensions, in brain regions exposed to the field of the three coils, recruiting variably-oriented neural structures. Yet, this hypothetical suggestion should be examined in future investigations.

Additional hypothetical advantage that may be gained by selective placement of coils in a multi-coil array (23) is that the efficiency of stimulation via the rotational field may be increased at depth where the fields from each coil overlap, while superficial levels of the cortex will mainly experience the field of only one of the coils. For example, a coil with slow rate of field attenuation with depth, such as the H7 coil, may be positioned over the medial motor cortex in P-A orientation. A second similar coil may be positioned over the orbitofrontal cortex in superior-inferior orientation. Operation of the two coils with a lag of ¼ a cycle will induce rfTMS in deeper medial PFC region, where the fields of the two coils overlap with similar intensity, while superficial regions underneath each coil experience mainly the field of one coil (Fig. S2). The actual effects are expected to depend on many factors, including the specific neural structure morphology, function and connectivity. Future modeling and neurostimulation studies will investigate both the absolute and relative effects in various brain regions including deep brain targets that can be achieved with such an approach.

In a previous multi-channel TMS study (23), we demonstrated that multiple pulses operation with sub-threshold conditioning pulse preceding a supra-threshold pulse by a few hundreds of microseconds leads to significant inhibition. A combined operation of coils with various depth profiles can increase the focality of TMS effect in deep brain regions, and this was demonstrated in the leg compared to the hand motor cortex (23). We suggest that the method outlined in this previous study may be combined with the current rfTMS concept to increase the selective effect in desired brain regions, including deep regions. As an example, a coil array based on the H7-coil similar to the one used in this study, may be used to apply rfTMS. Additional coils with fast attenuating depth profiles (such as small figure-8 coils) may be placed above that coils array, in which sub-threshold conditioning pulses are induced which precede the supra-threshold pulses of the H7-coil array by a few hundreds of microseconds. Under such conditions, superficial neural structures beneath the coils may experience inhibition due to the conditioning pulses, while deeper structures may be less affected by the fast-attenuating conditioning pulses; hence the rfTMS effect on these structures will be accentuated. Such an approach suggests a potential means to increase depth selectivity of stimulation that represents one of the main limitations of current TMS methodology, and may open the way to many novel applications in brain research and therapeutics that should be investigated in future blinded randomized studies.

Conflicts of interest

AZ and YR are inventors of deep TMS technology and have financial interest in Brainsway Ltd., a company that develops and commercialize deep TMS devices. GSP, MA, YH and AT are Brainsway employees. All other authors declare no competing interest.

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Figure Legends

Fig. 1. a. A sketch of the coil array over a human head, with the lower H7 coil (purple) and the upper coil (red). b. An image of the coil array.

Fig. 2. a. The electric field induced by two orthogonal coils having equal inductance, with a lag of a ¼ of a cycle between their operations. Two biphasic pulses are produced, and the resultant total field vector rotates and covers various orientations. b. A reconstruction of the effective electric field created from the sum of the two perpendicular coils, with the field of coil #1 directed along the y-axis and the field of coil #2 along the x-axis. The effective field completes

¾ of a full cycle during the magnetic pulses, as indicated by the gray arrows. The Latin numbers in squares indicate the order of evolvement of the field vector during the pulses in this case. The gray shade represents the generated field from angle 0° to 315° as defined in this study.

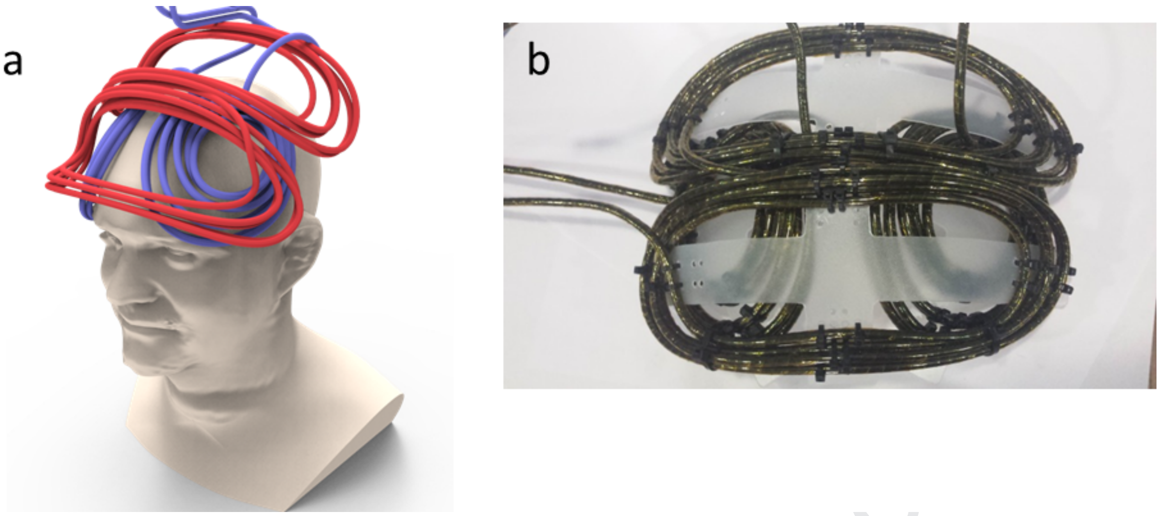
Fig. 3. Operation of a coil array with the two coils having the same orientation, where the upper coil is operated with a lag of a ¼ of a cycle after the lower coil. This way a conventional unidirectional electric field is induced, but with pulse duration of 1.25*(the cycle time of a single coil). The total field induced in the brain tissue is represented by the solid curve.

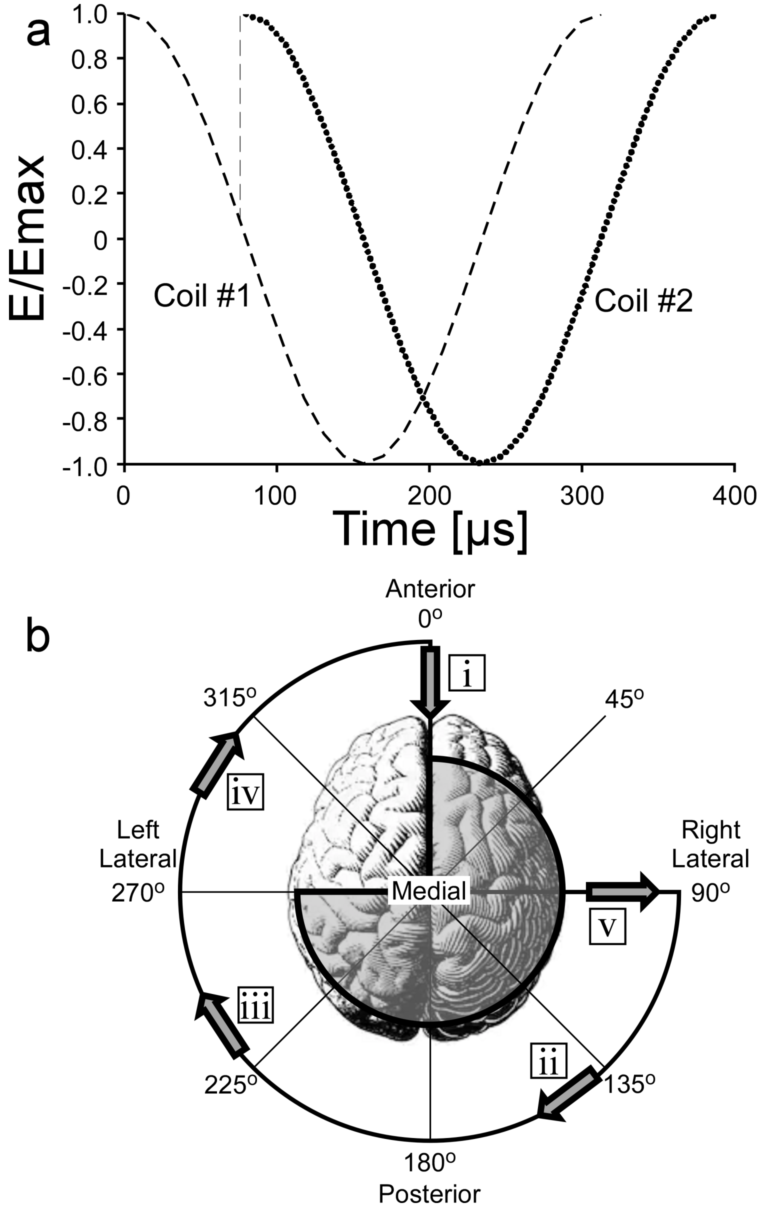
Fig. 4. Hand APB rMT for various udTMS orientations, and for four rfTMS states, relative to a single H7 coil oriented A-P (N=8). The black and white arrows represent the polarity induced during the second stroke of the biphasic pulse by the lower and upper coils, respectively. Shown are mean ± SE.

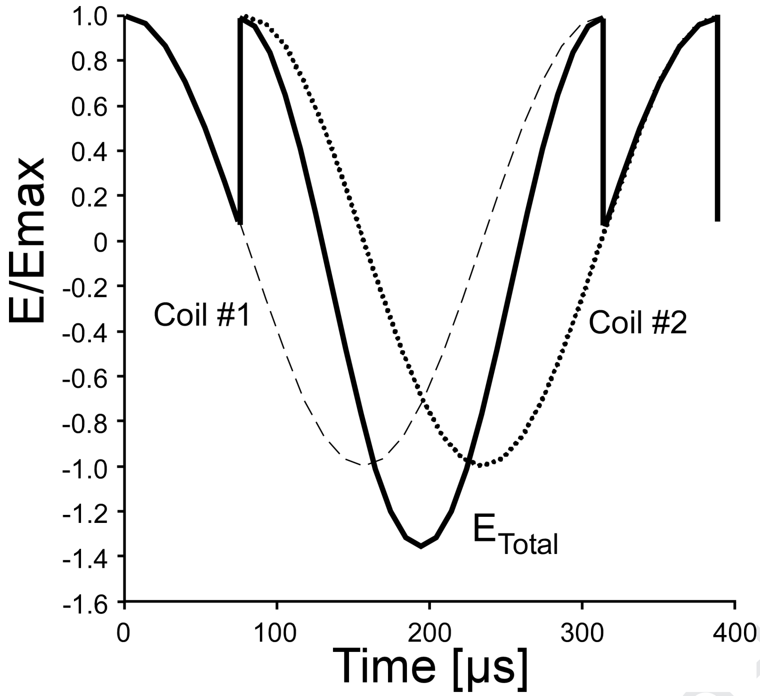
Fig. 5. Leg TA rMT for various udTMS orientations, and for four rfTMS states, relative to a single H7 coil oriented A-P (N=8). The black and white arrows represent the polarity induced during the second stroke of the biphasic pulse by the lower and upper coils, respectively. Shown are mean ± SE.

Fig. 6. Hand MEP at 120% of the rMT with the single H7 coil oriented A-P, for various udTMS orientations, and for four rfTMS states, relative to a single H7 coil oriented A-P (N=8). The black and white arrows represent the polarity induced during the second stroke of the biphasic pulse by the lower and upper coils, respectively. Shown are mean ± SE.

Fig. 7. Leg MEP at 120% of the rMT with the single H7 coil oriented A-P, for various udTMS orientations, and for four rfTMS states, relative to a single H7 coil oriented A-P (N=7; One of the subjects had a very high leg motor threshold for the upper coil and therefore 120% of that intensity was not feasible). The black and white arrows represent the polarity induced during the second stroke of the biphasic pulse by the lower and upper coils, respectively. Shown are mean ± SE.


a
b


a
1.0
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1.0
E/Emax
Coil #1
Coil #2
0
100
200
300
400
Time [µs]
b
Anterior
0°
i
45°
315°
iv
Left
Lateral
270°
Right
Lateral
90°
Medial
v
iii
ii
225°
135°
180°
Posterior


1.0
0.8
0.6
0.4
0.2
0
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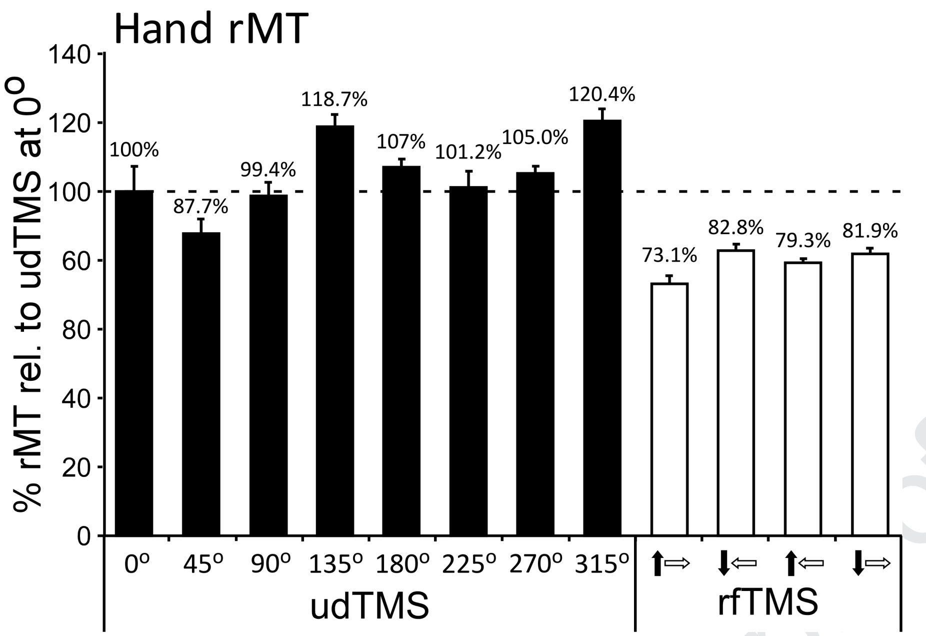
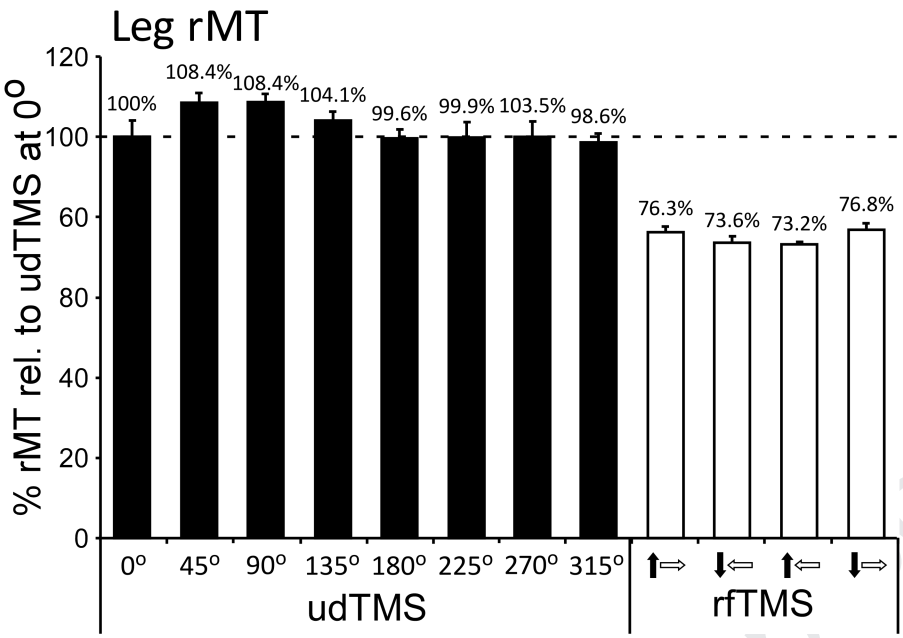
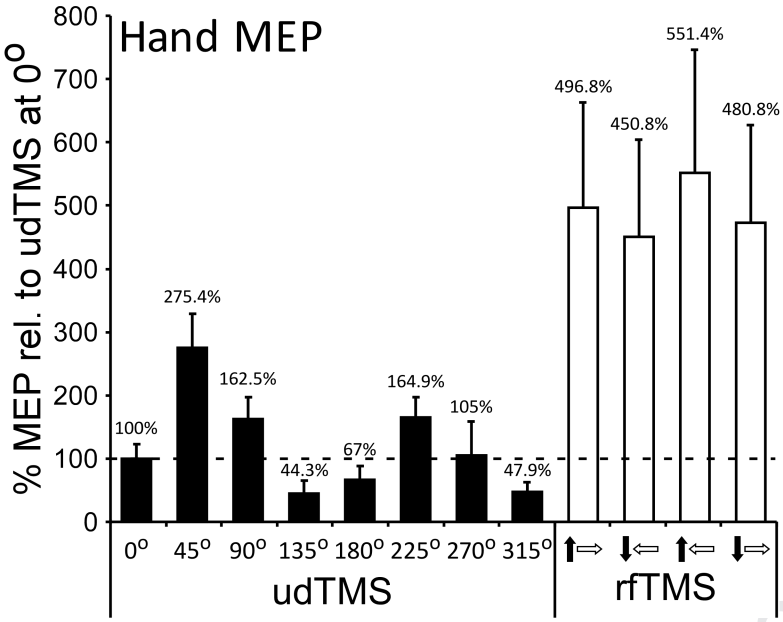
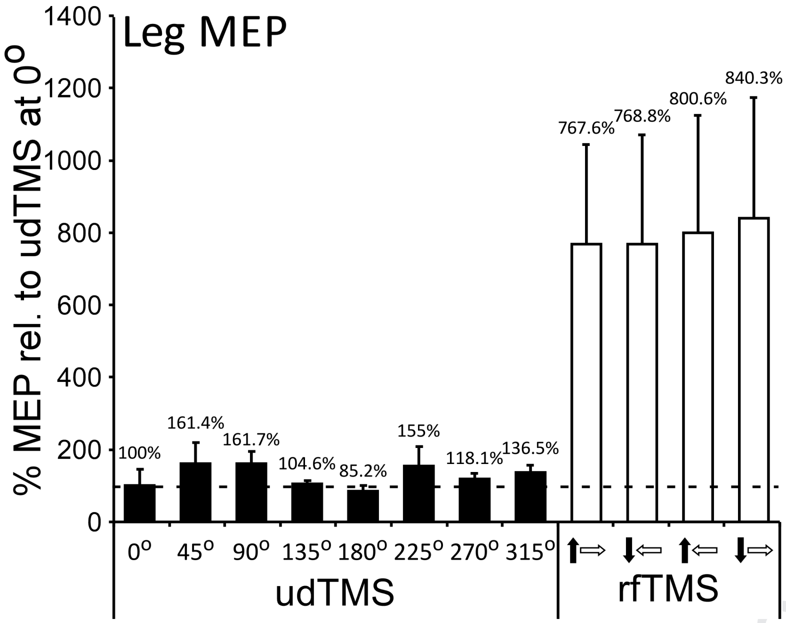
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
E/Emax
Coil #1
Coil #2
E_{Total}
0
100
200
300
400
Time [μs]


Hand rMT
% rMT rel. to udTMS at 0°
140
120
100
80
60
40
20
0
100%
87.7%
99.4%
118.7%
107%
101.2%
105.0%
120.4%
73.1%
82.8%
79.3%
81.9%
0°
45°
90°
135°
180°
225°
270°
315°
udTMS
rfTMS


Leg rMT
% rMT rel. to udTMS at 0°
120
100
60
80
40
20
0
100%
108.4%
108.4%
104.1%
99.6%
99.9%
103.5%
98.6%
76.3%
73.6%
73.2%
76.8%
0°
45°
90°
135°
180°
225°
270°
315°
udTMS
rfTMS



Hand MEP
% MEP rel. to udTMS at 0°
800
700
600
500
400
300
200
100
0
100%
275.4%
162.5%
44.3%
67%
164.9%
105%
47.9%
496.8%
450.8%
551.4%
480.8%
0°
45°
90°
135°
180°
225°
270°
315°
udTMS
rfTMS


Leg MEP
% MEP rel. to udTMS at 0°
1400
1200
1000
800
600
400
200
0
100%
161.4%
161.7%
104.6%
85.2%
155%
118.1%
136.5%
767.6%
768.8%
800.6%
840.3%
0°
45°
90°
135°
180°
225°
270°
315°
udTMS
rfTMS

HIGHLIGHTS

The study characterizes a novel method of rotational field TMS (rfTMS). Unique effects in both the hand and leg motor cortices are demonstrated. RMTs and MEPs were compared to conventional TMS applied at different orientations. rfTMS produced significantly lower RMTs and higher MEPs in both motor cortices. Potential benefits and applications of rfTMS are discussed.

Conflicts of interest

AZ and YR are inventors of deep TMS technology and has financial interest in Brainsway Ltd., a company that develops and commercialize deep TMS devices. GSP, MA, YH and AT are Brainsway employees. All other authors declare no competing interest.

Author contribution statement.

Yiftach Roth: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review&editing. Gaby S Pell: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review&editing. Noam Barnea-Ygael: Writing - original draft, Writing - review&editing. Moria Ankry: *Investigation ;Project administration; Resources*; *Data curation;* Writing - review&editing. Yafit Hadad: *Investigation; Data curation;* Writing - review&editing. Ami Eisen: Conceptualization, Methodology; Writing - review&editing. Yuri Burnishev: Conceptualization, Methodology; Writing - review&editing. Aron Tendler: *Conceptualization ;Writing - original draft; Writing - review & editing*. Elisha Moses: Conceptualization, Methodology ; Writing - original draft ;Writing - review&editing. Abraham Zangen: Conceptualization, Methodology, Writing - review&editing, Supervision