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RESEARCH NOTE

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Transcranial magnetic stimulation

Which part of the current waveform causes the stimulation?

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Abstract To investigate the mechanism of transcranial magnetic stimulation (TMS), we compared the directional effects of two stimulators (Magstim 200 and Magstim Super Rapid). First, stimulating visual cortex and facial nerve with occipital mid-line TMS, we found that, for a particular coil orientation, these two stimulators affected a particular neural structure in opposite hemispheres and that, to affect a particular neural structure in a particular hemisphere, these two stimulators required opposite coil orientations. Second, stimulating a membrane-simulating circuit, we found that, for a particular coil orientation, these two stimulators resulted in a peak induced current of the same polarity but in a peak induced charge accumulation of opposite polarity. We suggest that the critical parameter in TMS is the amplitude of the induced charge accumulation rather than the amplitude of the induced current. Accordingly, TMS would be elicited just before the end of the first (Magstim 200) and second (Magstim Super Rapid) phase of the induced current rather than just after the start of the first phase of the induced current.

Keywords Transcranial magnetic stimulation · Mechanism · Waveform · Human

Introduction

Transcranial magnetic stimulation (TMS) is assumed to occur via the electric currents that are induced by the time-varying magnetic field (Barker et al. 1985), but the neurophysiology is still largely unknown. The same is true for the neuroanatomy, although visual hemi-field (VHF) scotomas and early eye-blinks can be assumed to be elicited at some point along the contra-lateral visual pathway (Amassian et al. 1989) and the ipsi-lateral facial nerve (Ghezzi et al. 1992), respectively, when elicited by occipital mid-line TMS.

During occipital mid-line TMS experiments to be reported elsewhere, circumstances forced us to replace a Magstim Super Rapid with a Magstim 200, leading to the unexpected finding that, for the same direction of current direction indicating (CDI) arrows marked on the coil, these two stimulators induced scotomas in the opposite VHF. Because these arrows are meant to indicate the direction of the coil current during its initial rise, this finding suggested either that these arrows were correct for only one stimulator or that the initial rise of the coil current did not cause the TMS effect for at least one stimulator. Subsequent use of a CDI probe showed that the CDI arrows were correct for both stimulators.

The present set of experiments had three goals. First, to see if we could confirm that these two stimulators resulted in opposite directional occipital mid-line TMS effects: the stimulators were now compared under identical experimental conditions, for two neural structures (visual cortex and facial nerve), and for two directions of the CDI arrows (leftwards and rightwards). Second, to see if we could confirm that these two stimulators resulted in an initial induced current of the same direction: induced current direction was now assessed more directly with a search coil and an oscilloscope. Note that the polarity of the initial (–/+ cosine quarter-cycle) induced current is opposite to the polarity of the initial (+/– sine quarter-cycle) coil current, but that the former is the same for the two stimulators if and only if the latter is. Third, if both findings were confirmed, to seek an explanation of this apparent paradox.

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Material and methods

Experiment 1A

The subjects were ten students. The experiments were conducted with written informed consent of each subject and with the approval of the departmental ethics committee. Visual stimuli were ten single letters displayed for 1 refresh cycle on a Sony 200 GST monitor (visual stimulus duration less than 2 ms). They were viewed at a distance of 56 cm, subtending 0.3 ° at a lateral eccentricity of 1.0 °, either to the left or to the right of the fixation point. The luminance of the letters and their background was 0 cd.m^{-2} and 40 cd.m^{-2}, respectively. Magnetic stimuli were generated with a 90 mm ring sandwich coil (a 90 mm mean diameter circular coil that consists of two circular coils placed on top of each other) and either a Magstim 200 or a Magstim Super Rapid (stimulators that generate a mono-phasic and bi-phasic coil current, respectively). The output of both stimulators was set to 90% of their maximum output. The coil position was the same for all trials: the coil was held in a near-frontal plane with its centre in the mid-sagittal plane, with its handle pointing upwards, and with only its lower rim held against the head, 2–3 cm rostral to the inion. However, the coil orientation varied between two states: a 180° rotation about the longitudinal axis of its handle changed the side of (the lower rim of) the coil that was held against the head so that the CDI arrows were directed either to the left or to the right hemisphere. Note that with a figure-of-eight coil, the direction of the CDI arrows does not change with such a rotation, because this coil consists of two circular adjacent co-planar coils that are on opposite side of the longitudinal axis of its handle and that have currents running in opposite directions. The delay varied between two values: the onset of the magnetic stimulus was either 500 ms earlier (control delay) or 100 ms later (test delay) than the onset of the visual stimulus. Subjects had their heads stabilised in a chin and forehead rest and were asked to identify each letter. Each subject was tested with 8 blocks of 40 trials, with 2 blocks for each of 4 conditions (2 stimulator types × 2 coil orientations); the order of the conditions was pseudo-random and different for each subject. Each block tested the effect of the two VHFs with each of the two delays and with each of the ten letters; the order of a particular VHF, delay and letter was random and different for each block. Rate of occurrence of visual suppression was calculated by subtracting the error rate at the control delay from the error rate at the test delay. *P*-values for differences in rate of occurrence of visual suppression between two conditions were calculated with a one-tailed paired *t*-test.

Experiment 1B

The subjects were ten students. The experiments were conducted with written informed consent of each subject and with the approval of the Departmental Ethics Committee. Magnetic stimuli were generated and applied as before, except that the output of the two stimulators was set to 70%, 80% and 90% of their maximum output. Subjects had their head stabilised in a chin and forehead rest. On each trial, left and right eyes were monitored simultaneously with a high-speed Kodak Ektapro EM video system to detect an early blink (temporal resolution, 2 ms; spatial resolution, less than 0.5 mm); blink amplitude was not measured. Each subject was tested with 12 blocks of 2 trials, with one block for each of 12 conditions (2 stimulator types × 2 coil orientations × 3 stimulator intensities); the order of the conditions was pseudo-random and different for each subject. *P*-values for differences in rate of occurrence of detected early blinks between two conditions were calculated with a one-tailed paired *t*-test.

Experiment 2

Magnetic stimuli were generated with a 90 mm ring sandwich coil and either the Magstim 200 or the Magstim Super Rapid and applied to a search coil that was connected to an electric circuit. This electric circuit consisted of a resistor R_l=100 kΩ (representing longitudinal axonal resistance) in series with a parallel resistor R_m=1 kΩ and capacitor C_m=0.15 μF (representing membrane resistance and capacitance, respectively). Note that these values are not critical but were chosen to approximate the high longitudinal axonal resistance and a realistic membrane time constant (Barker et al. 1991). Both the search coil electromotive force (EMF) and the voltage across the parallel R_mC_m network (with time constant R_mC_m=150 μs) were recorded by an oscilloscope. We also recorded the voltage across C_m (with R_m set to infinity).

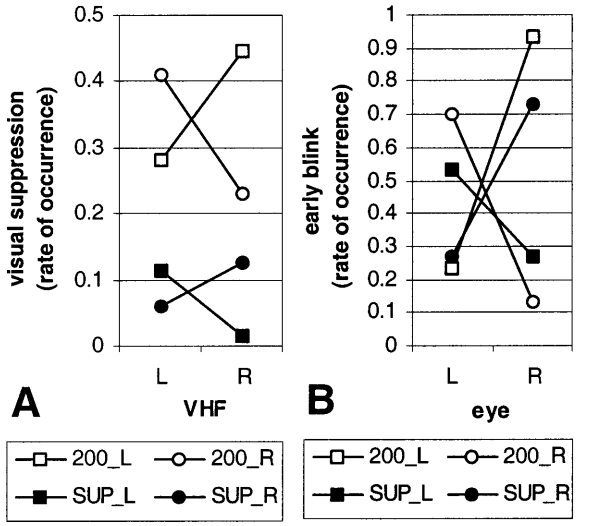

Fig. 1 **a** Rate of occurrence of visual suppression for left (*L*) and right (*R*) visual hemi-field (*VHF*) averaged over ten subjects; each of the eight symbols is the mean of 200 entries. **b** Rate of occurrence of early blinking for left (*L*) and right (*R*) eye (*eye*) averaged over three intensities and ten subjects; each of the eight symbols is the mean of 60 entries. Both **a** and **b** show data for both Magstim 200 (*200*) and Magstim Super Rapid (*SUP*) and for current direction indicating arrows on the coil pointing to both left (*_L*) and right (*_R*) hemisphere

Results

Results of experiment 1 are shown in Fig. 1. Figure 1a shows the mean rate of occurrence of visual suppression and Fig. 1b shows the mean rate of occurrence of early blinking. Note that for each neural structure (visual cortex and facial nerve), 12 single-variable comparisons follow, 4 for stimulator type (Magstim 200 versus Magstim Super Rapid), 4 for CDI direction (leftwards versus rightwards), and 4 for hemisphere (left versus right), but that only the last 8 concern purely directional effects.

For left VHF/eye, Magstim 200 was more effective with rightwards than with leftwards CDI (P=0.026/P<0.001), and Magstim Super Rapid was more effective with leftwards than with rightwards CDI (P=0.073/P=0.001). For right VHF/eye, Magstim 200 was more effective with leftwards than with rightwards CDI (P=0.012/P<0.001), and Magstim Super Rapid was more effective with rightwards than with leftwards CDI (P=0.035/P<0.001).

With leftwards CDI, Magstim 200 affected more right than left VHF/eye (P=0.022/P<0.001), and Magstim Super Rapid affected more left than right VHF/eye (P=0.016/P=0.009). With rightwards CDI, Magstim 200 affected more left than right VHF/eye (P=0.024/

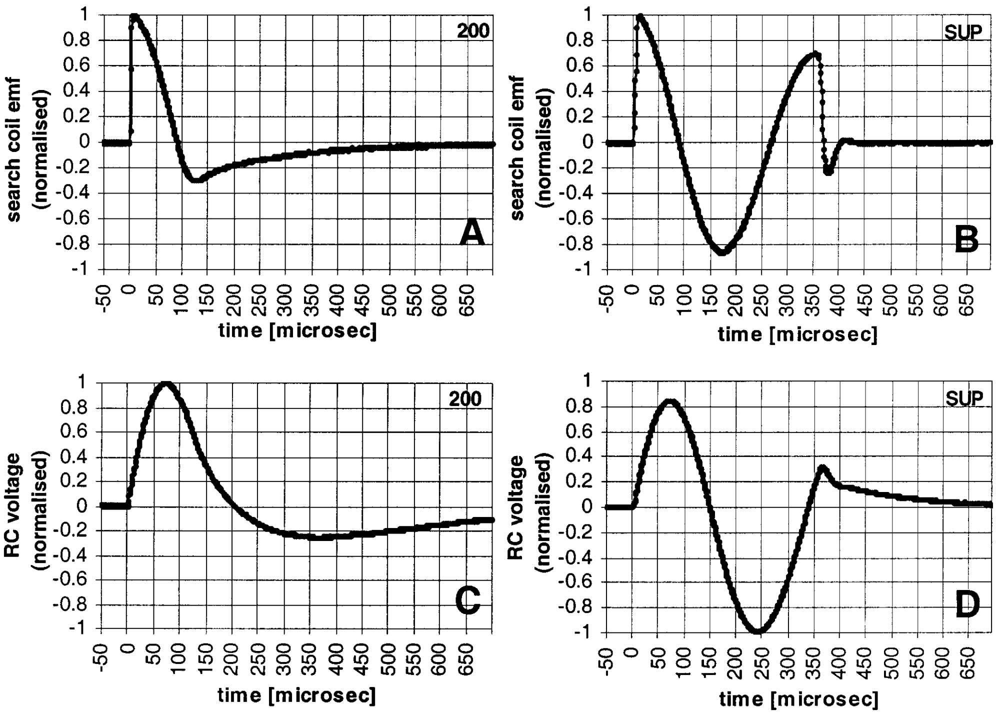

Fig. 2 **a, b** Signals are proportional to the search coil EMF (and thus to the current which would be induced in the tissue) as a function of time, for the Magstim 200 and the Magstim Super Rapid, respectively. **c, d** Signals are proportional to the voltage across the parallel $R_m C_m$ network (and thus to the induced charge which would accumulate on a membrane with a time constant of 150 µs) as a function of time, for the Magstim 200 and the Magstim Super Rapid, respectively

P<0.001), and Magstim Super Rapid affected more right than left VHF/eye (P=0.079/P<0.001).

Results of experiment 2 are shown in Fig. 2. Signals in Fig. 2a, b are proportional to the search coil EMF (and thus to the current which would be induced in the tissue) as a function of time, for the Magstim 200 and the Magstim Super Rapid, respectively. Signals in Fig. 2c, d are proportional to the voltage across the parallel $R_m C_m$ network (and thus to the induced charge which would accumulate on a membrane with a time constant of 150 µs) as a function of time, for the Magstim 200 and the Magstim Super Rapid, respectively. For the Magstim 200, induced current at its first/second phase peak was +1.00/–0.31 and induced charge accumulation at its first/second phase peak was +1.00/–0.26. For the Magstim Super Rapid, induced current at its first/second phase peak was +1.00/–0.87 and induced charge accumulation at its first/second phase peak was +0.84/–1.00. For the Magstim Super Rapid, numerical integration with respect to time (area under curve) of the induced current for its first/second phase was +52.12/–96.80. With R_m set to infinity (data not shown), for the Magstim Super Rapid, induced charge accumulation at its first/second phase peak was +1.00/–0.82.

Discussion

In experiment 1, we applied occipital mid-line TMS with two stimulator types (Magstim 200 and Magstim Super Rapid) and two coil orientations (leftwards and rightwards CDI) and assessed the effects on two neural structures (facial nerve and visual cortex) in two hemispheres (left and right). We found two asymmetries that showed that the directional TMS effects of the two stimulator types were opposite. First, for both neural structures and for both coil orientations, we found that, for a given neural structure and for a given coil orientation, the most affected hemisphere was opposite for the two stimulator types. Second, for both neural structures and for both hemispheres, we found that, for a given neural structure and for a given hemisphere, the most effective coil orientation was opposite for the two stimulator types. To our knowledge, the first stimulator type directional asymmetry has not been reported before and the second stimulator type directional asymmetry has not been reported before for either the visual cortex or the facial nerve, although it has just been reported for the left motor cortex (Kammer et al. 2001). Note that, from the 16 single-variable comparisons presented in the Results, 6 of such two-variable interactions follow: in addition to these two for stimulator type, there are also two for neural structure, 1 for CDI direction, and 1 for hemisphere; all appear as asymmetries. To our knowledge, the two directional asymmetries between the two neural structures are (the only remaining) new findings. First, for both stimulators and for both coil orientations, we found that, for a given stimulator and for a given coil orientation, the most affected hemisphere was opposite for the two neural structures. Second, for both stimulators and for both hemispheres, we found that, for a given stimulator and for a given hemisphere, the most effective coil orientation was opposite for the two neural structures. It is not inconceivable that these neural structure directional asymmetries could be explained in part by location and/or orientation differences between the stimulated fibers of the two neural structures. The importance of asymmetries is potentially greater than just a practical one, as they can provide insight into the mechanism of TMS. In this study we tried to investigate the stimulator type directional asymmetries.

In experiment 2, we applied the magnetic stimulus to an electric circuit that contained a parallel resistor R_m and capacitor C_m with R_mC_m=150 µs, simulating a neuronal membrane in the human cortex under sub-threshold conditions (Barker et al. 1991). We found that the induced current at its maximum amplitude had the same the polarity for the two stimulators, but that the induced charge accumulation at its maximum amplitude had the opposite polarity for the two stimulators. First, the induced current (and thus also the induced charge accumulation) in its first phase had the same polarity for the two stimulators. Second, the induced current reached its maximum amplitude in its first phase for both the Magstim 200 and the Magstim Super Rapid. Third, the induced charge accumulation reached its maximum amplitude in its first phase for the Magstim 200 but in its second phase for the Magstim Super Rapid.

Comparison of the stimulator type asymmetry results of experiment 1 with the polarity (dis)parity results of experiment 2, suggests that the critical parameter for achieving TMS is more likely to be the amplitude of the induced charge accumulation than the amplitude of the induced current. This proposition is not inconceivable, as the initiation of action potentials depends on the opening of sodium channels, as the opening of sodium channels depends on the potential of the neuronal membrane, and as the potential of the neuronal membrane as a (lossy) capacitor depends on its charge.

The key finding that, for the Magstim Super Rapid induced charge accumulation, peak amplitude was lower in its first than in its second phase (ratio 0.84:1.00) can be explained by the presence of a resistance R_m. Indeed, with R_m set to infinity, for the Magstim Super Rapid induced charge accumulation, peak amplitude was higher in its first than in its second phase (ratio 1.22:1.00). This explanation is also suggested by the finding that for the Magstim Super Rapid induced current, the area under its first phase was larger than the difference in area between its second and its first phase (ratio 1.17:1.00). Note that the area under the curve of the induced current, summed up to a particular point in time, is equal to the net charge that would be accumulated at that time by this induced current on a lossless membrane.

Consideration of the following four cases might be illustrative. With a lossless (zero series resistance) stimulator and a lossless (infinite parallel resistance) membrane, peak amplitude of the induced charge accumulation would be equal in its first and second phase. Indeed, with a lossless stimulator, the area under the first phase of the induced current would be exactly half the area under the second phase and, with a lossless membrane, all induced current would flow through the membrane capacitance, increasing and decreasing the accumulated charge according to its quarter-cycle. With a lossy stimulator and a lossless membrane, peak amplitude of the induced charge accumulation would be higher in its first than in its second phase, as we found in experiment 2 with R_m set to infinity. Indeed, with a lossy stimulator, the area under the first phase of the induced current would be larger than the difference in area between the second and the first phase. Even with a lossy stimulator, with a lossy membrane, peak amplitude of the induced charge accumulation can be lower in its first than in its second phase, as we found in experiment 2, with R_mC_m=150 µs. Indeed, with a lossy membrane, current will flow through the membrane resistance, leaking charge accumulated on the membrane capacitance, tending to decrease the accumulated charge at any time. Because the charge accumulation set up during the first phase of the induced current thus leaks away, it is neutralized earlier into the second phase of the induced current such that the charge accumulation set up during the remainder of the second phase of the induced current can be larger. An induced current consisting of a quarter-cycle first phase, a half-cycle second phase, and a quarter-cycle third phase can thus result in more depolarisation with a hyperpolarising first phase and depolarising second phase than with a depolarising first phase and a hyperpolarising second phase. This agrees with findings of recent theoretical (Davey and Epstein 2000) and in vitro (Maccabee et al. 1998) studies.

In conclusion, these experiments appear to have both a practical and a theoretical implication. Experiment 1 indicated that the most affected hemisphere can vary not only with the coil orientation but also with the stimulator type and the neural structure, and that the most effective coil orientation can vary not only with the hemisphere but also with the stimulator type and the neural structure. Experiments 1 and 2 together indicated that the critical parameter for achieving TMS is more likely to be the amplitude of the induced charge accumulation than the amplitude of the induced current.

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