Suppression of vision by transcranial magnetic stimulation: a third mechanism

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INTRODUCTION

Three separate periods have been described when single-pulse transcranial magnetic stimulation (TMS) of the occipital pole can impair vision. Such TMS-induced suppression occurs maximally when the magnetic stimulus precedes the visual stimulus by 50–70 ms (dip 0) and when the magnetic stimulus follows the visual stimulus by 20–30 ms (dip 1) and by 80–120 ms (dip 2). Dip 0 is best explained by a reflex eye closure, whereas dip 1 and dip 2 are best explained by a disruption of letter-processing neural activity in the underlying visual cortex.

New experiments revealed TMS-induced suppression that occurred maximally at times between those of dip 0 and dip 1. To investigate this further, we used different TMS intensities to try to differentiate the possibly different TMS effects and infrared eye monitoring to reveal the precise timing of TMS-induced eye closure.

MATERIALS AND METHODS

Subjects were aged 18–25 years, free of any neurological condition and had normal vision except for a corrected mild myopia. The experiments were conducted with the informed consent of each subject and with the approval of the Departmental Ethical Committee.

Magnetic stimuli were delivered with a Magstim Model 200 stimulator (Magstim Company Ltd, Wales, UK) and a 90 mm ring sandwich coil. The coil was centred on the mid-sagittal line with its lower rim tangential to the scalp and with the lower edge of the lower rim 1 cm rostral to the upper edge of the inion. Subjects wore latex bathing caps to mark and monitor the position of the coil. The intensity of the stimulator ranged from 65% to 80% of its maximum output.

Visual stimuli were ten letters (A, B, E, N, O, S, U, V, X, Z) displayed in upper case Arial font, each subtending 0.35° visual angle at the viewing distance of 50 cm. The letters were displayed in black (0.01 cd m⁻²) against a grey (10.4 cd m⁻²) background on a Sony 200 GST monitor, set to a 1024 x 768 resolution mode and to a 100 Hz vertical refresh rate.

The delay, defined as time of onset of the magnetic stimulus minus time of onset of the visual stimulus, was varied in steps of 10 ms and ranged from -70 ms to 170 ms or from -90 ms to 50 ms. The TMS pulse produces an electronic artefact on the monitor screen. The position of the magnetic stimulus artefact relative to the position of the visual stimulus is the same for all tested delays (as the monitor is set to 100 Hz and as the delay is varied in steps of 10 ms). The relative timing, of course, does vary with the delay. A spatial coincidence of artefact and letter could thus result in a systematic masking for a subset of delays, and could thus result in an artificial dip in the performance curve. To prevent this, 2 ms were added to each delay so that the artefact was always located 1/5th of the screen height below the letter.

The sequence of both letters and delays was randomized with the constraint that each delay was tested exactly once with each of the ten letters. Sequences were randomized anew for each session. Stimulus presentation was controlled by PicBlit3.6 software [11]. On each trial, the subject saw the following sequence of events: a grey screen, a superimposed black fixation cross for 50 refresh cycles, a
grey screen for 50 refresh cycles, a superimposed black letter for one refresh cycle, and a grey screen. The subject had to identify each letter, by guessing if necessary. They were rewarded according to their performance by receiving 10 pence for every correct response.

In a second set of experiments, we studied TMS-induced changes in the eyelid position with a temporal resolution of 1 ms by means of a Skalar Iris 6500 infrared eye tracker. TMS was applied as before while subjects performed a similar letter-identification task.

In a third set of experiments, we measured the duration of the visual stimulus and the timing between the visual stimulus and the magnetic stimulus by means of a 2-channel storage oscilloscope and a diode (rise time < 150 µs).

RESULTS

Figure 1a shows the two performance curves that initiated this investigation: the two subjects (S1, S2) who were tested with 25 delays (at a TMS intensity of 70%) showed very different curves. Subject 2 shows only one dip: this dip is deepest at −70 ms and has ended at −20 ms. Subject 1 shows, in addition to a hint of this dip at −70 ms, and in addition to a dip that is deepest at +100 ms, a dip that is deepest at −20 ms and that has ended at +40 ms. Subsequently reducing the number of delays to 15 (allowing 20 instead of 10 trials per delay), we found that subjects followed one of these two patterns at this TMS intensity: two subjects (S1, S3) showed maximal suppression at −20 ms and three subjects (S2, S4, S5) did not show suppression at this delay. We then further investigated

Fig. 1. Curves show proportion of visual stimuli correctly identified as a function of delay. Delay is defined as time of onset of the magnetic stimulus minus time of onset of the visual stimulus: negative values thus indicate that the magnetic stimulus preceded the visual stimulus. Chance level is 10%, indicated by a thin line. Subject and TMS intensity are indicated in the accompanying boxes. Every symbol is the mean of 10 (a) or 20 (b–d) trials. Error bars denote 1 s.e.m. (a) Initial two curves (subject 1 and 2). (b) Curves of subjects 2, 4, and 5. (c) Curves of subject 3 at different TMS intensities. (d) Curves of subject 1 at different TMS intensities.
subjects S1 and S3 at both higher and lower TMS intensities.

Figure 1b shows the performance curves for subjects 2, 4, and 5. The three curves show a clear dip whose uphill slope starts at −70 ms and has ended at −20 ms. Figure 1c shows the performance curves for subject 3 at three different TMS intensities. At 65%, the uphill slope starts at −30 ms and has ended at +10 ms; at 70%, the uphill slope starts at −20 ms; and at 80%, the uphill slope starts at +10 ms. Figure 1d shows the performance curves for subject 1 at four different TMS intensities. At 65%, the uphill slope starts at −70 ms and has ended at −20 ms; at 70%, the uphill slope starts at −20 ms; at 75%, the uphill slope starts at 0 ms; and at 80%, the uphill slope starts at +20 ms.

Figure 2a is a readout of the infrared recording for subject 4. It shows an early unilateral blink (on the right-hand side) and a late bilateral blink. Figure 2b shows the mean and the range of the latency of the early and the late eyelid motion for all four subjects (S4, S6, S7, S8). The shortest latencies were 11 ms, 12 ms, 9 ms and 11 ms for the early blink and 24 ms, 34 ms, 42 ms and 38 ms for the late blink.

Measurement of the duration of the visual stimulus showed that pixel illumination decreased to an undetectable level (<5% of maximum illumination) less than 1.2 ms (± 0.1 ms) after its onset. Measurement of the delay mismatch showed that the magnetic stimuli came 1.80 ms (± 0.05 ms) later than indicated on the X-axis of the performance curves.

**DISCUSSION**

Three of five subjects (S2, S4, S5) showed TMS-induced suppression at previously observed times: a dip with an uphill slope from −70 to −20 ms. However, the other two subjects (S1, S3) showed performance curves with three surprising features. First, the uphill slope of one curve started at −30 ms and had ended at +10 ms. Second, the uphill slope of four other curves started at −20 ms, 0 ms and +10 ms. Third, the curves showed a right-shift of (the start of) their uphill slopes from −20 ms to +20 ms with increasing TMS intensity. None of these three features can be explained by a direct disruption of letter-processing neural activity and/or by a blink-associated covering of the pupils.

First, it is difficult to explain the data via a direct disruption of letter-processing neural activity. Suppression occurring up to a delay of 0 ms but not later, and local maxima of suppression occurring at delays of −20 ms and 0 ms are difficult to explain by a disruption of neural activity that starts not earlier than 20 ms after the presentation of the letter [1]. A right-shift of the uphill slope (extending maximal suppression to later delays) is difficult to explain by a disruption of neural activity because an increase in TMS intensity leads in fact to an extension of maximal suppression to earlier delays (leaving the position of the uphill slope unchanged). It is this effect that prevented these two subjects from reaching maximum performance at +40 ms and +50 ms: an increased TMS intensity resulted in an increased duration of the TMS effect so that dip 2 (centred at about +100 ms) was already elicited at these early delays.

Second, it is difficult to explain the data via a covering of the pupils. The technical measurements that showed that the visual stimulus had ended 1.2 ms after its onset and that the onset of the magnetic stimulus occurred 1.8 ms later than indicated by the X-axis, allow us to rule out...
covering of the pupils as a cause of suppression for a delay of 0 ms. Indeed, for a delay of 0 ms, the visual stimulus had ended 0.6 ms before the onset of the magnetic stimulus: the letter was therefore fully presented on screen before even the start of the process that elicited the blinking. The infrared measurements that showed an early blink with a latency of 9–13 ms, in addition to a late blink with a latency of 24–49 ms, suggest that covering of the pupils is not a likely cause of suppression for the delays of −10 ms and −20 ms either. Indeed, for a delay of −10 ms, the visual stimulus had ended 9.4 ms after the onset of the magnetic stimulus: the letter was therefore fully presented on screen either before the eyelid had started moving or < 1 ms after the eyelid had started moving. As the average downward velocity of the eyelid is of the order of only 0.2 mm/ms [12], a (slower) initial 1 ms of motion is not likely to induce optical interference. For a delay of −20 ms, covering of the pupils does not seem a likely cause of suppression as the early blink is both small and unilateral and as the late blink has a latency > 20 ms. In conclusion, covering of the pupils cannot cause (a local maximum of) suppression at a delay of 0 ms (and probably not even at a delay of −10 ms and −20 ms). A right-shift of uphill slopes with an increase in TMS intensity (that could occur via a shortening of the latency of blinking) would thus also occur at earlier (more negative) delays than actually observed.

Third, it is difficult to explain the data via a combination of the effects of the two aforementioned mechanisms. If two mechanisms result in suppression that is additive and that occurs at a common subset of delays, then a local maximum of suppression could occur at a delay that is part of this common subset of delays and that is between the delays of the two respective local maxima. However, this possibility can still not explain, for example, a local maximum at a delay of 0 ms because this delay is not part of the common subset of delays.

We think the data are best explained if in addition to the previously described [2] high-sensitivity dip 0 centred at about −70 ms and the low-sensitivity dip 1 centred at about −20 ms, there is an intermediate-sensitivity dip centred at about −20 ms (dip X). Indeed, the three features of the data follow immediately from (the sequential super-position of) three such dips. At the lowest TMS intensity, subject 1 shows an isolated dip 0 whereas subject 3 already shows the addition of a dip 0 with a dip X. With increasing TMS intensity, these two subjects add a dip 1, resulting in a right-shift of (the start of) the total dip. We see several possible mechanisms via which TMS could result in a dip X. (Current experiments to be reported provide further support for the previously hypothesised mechanisms for dip 0 and dip 1.)

First, a direct disruption of neural activity could explain a dip X if it involved some pre-letter activity (as opposed to post-letter processing activity) starting 20 ms before the presentation of the letter. However, as subjects were presented with a 500 ms blank between the fixation point and the letter, this would imply that the brain is able to measure 480 ms out of 500 ms, and this does not seem likely. We also failed to find evidence in the literature for such neural activity.

Second, TMS results in an audible click and a tingling feeling and the processing of these stimuli could interact with, and thus possibly suppress, the processing of the letter, especially as intersensory interaction has been previously reported with TMS [13,14]. However, as this intersensory interaction was a facilitation (of a reaction-time test), and as we failed to find evidence in the literature for visual suppression with such auditory or somatosensory stimuli, intersensory suppression does not seem a likely explanation.

Third, TMS results in a screen artefact and the processing of this stimulus could interact with, and thus possibly suppress, the processing of the letter. However, because of the programmed delay mismatch (see above), such intersensory suppression does not seem a likely explanation.

Fourth, as with direct electrical stimulation of the striate cortex [15], occipital TMS can result in phosphenes [7,8], indicating that TMS can induce ionic currents in the early visual cortex that are processed into visual percepts of various form and colour. At a delay of −20 ms the initial TMS-induced ionic currents are about 40 ms too early to interfere with the initial letter-induced ionic currents, but the subsequent processing of the former could interact with, and thus possibly suppress (the processing of) the latter. However, this mechanism does not seem a likely explanation, especially as none of the subjects reported any phosphenes.

Fifth, similar to direct electrical stimulation of the striate cortex [16,17], TMS could elicit saccades, and these saccades could suppress vision via an optical or a central mechanism. Optical interference can be ruled out because, even more so than with blinks (see above), elicited saccades would occur too late. But also a saccade-associated suppression of central vision does not seem a likely explanation as TMS was shown to be unable to elicit saccades in several studies [5,18–20].

Sixth, TMS elicits blinking and these blinks could suppress vision via a central mechanism. It has indeed been shown that blinks, voluntary [12] as well as reflex [21], are associated with a suppression of central vision, and that this suppression is maximal when the onset of the visual stimulus coincides with [12] or precedes by 30 ms [21] the onset of the blink. Such a suppression is more likely to be associated with the late (polysynaptic reflex) blink than with the early blink that is due to just a direct stimulation of the facial nerve [22–24], and would thus be maximal if TMS preceded the letter within a 40 ms interval. The observation that subject 4 showed a late blink but no noticeable suppression (no dip X) may pertain to the finding that the amount of suppression is (positively) related to the blink amplitude, as well as to the finding that this relation seems to show substantial interindividual variability [25].

CONCLUSION

We found TMS-induced suppression of vision that is difficult to explain via a covering of the pupils or via a direct interference with letter-processing neural activity; it points instead to a direct interference with pre-letter neural activity or to a non-direct interference with letter-processing neural activity. TMS induces a cascade of events such that the resulting behavioural outcome can be caused not only via a direct effect upon the underlying neural activity but also via several non-direct effects; the mechanism may
be determined by appropriate control conditions and/or additional imaging techniques.

REFERENCES

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