Exp Brain Res (2005) 160: 118–128
DOI 10.1007/s00221-004-1991-1

RESEARCH ARTICLES

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Transcranial magnetic stimulation in the visual system. I. The psychophysics of visual suppression

Received: 2 June 2003 / Accepted: 17 May 2004 / Published online: 11 September 2004

Abstract When applied over the occipital pole, transcranial magnetic stimulation (TMS) disrupts visual perception and induces phosphenes. Both the underlying mechanisms and the brain structures involved are still unclear. The first part of the study characterizes the suppressive effect of TMS by psychophysical methods. Luminance increment thresholds for orientation discrimination were determined in four subjects using an adaptive staircase procedure. Coil position was controlled with a stereotactic positioning device. Threshold values were modulated by TMS, reaching a maximum effect at a stimulus onset asynchrony (SOA) of approx. 100 ms after visual target presentation. Stronger TMS pulses increased the maximum threshold while decreasing the SOA producing the maximum effect. Slopes of the psychometric function were flattened with TMS masking by a factor of 2, compared to control experiments in the absence of TMS. No change in steepness was observed in experiments using a light flash as the mask instead of TMS. Together with the finding that at higher TMS intensities, threshold elevation occurs even with shorter SOAs, this suggests lasting inhibitory processes as masking mechanisms, contradicting the assumption that the phosphene as excitatory equivalent causes masking. In the companion contribution to this one we present perimetric measurements and phosphene forms as a function of the stimulation site in the brain and discuss the putative generator structures.

Keywords Occipital cortex · Visual masking · Threshold modulation · Psychometric function · Slope

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Introduction

Since its first description by Amassian et al. (1989) the application of transcranial magnetic stimulation (TMS) to the visual cortex with the resulting disruption of visual processes has evolved into a key example of TMS as a reversible, functional lesion technique. When combined with precise navigational techniques, TMS allows the characterization of different stages of cortical information processing with good spatial specificity and high temporal accuracy. The model of TMS-induced lesions in the visual system can in turn be used to characterize the effects of TMS on cortical processing in more detail.

Amassian et al. (1989) postulated that inhibitory processes, in particular inhibitory postsynaptic potentials induced by a TMS pulse, cause the visual suppression effect. From the motor system we know that a TMS pulse induces both excitation in the form of muscle twitches (Barker et al. 1985) and inhibition, such as the cortical silent period after a twitch in the preinnervated muscle (Fuhr et al. 1991; Inghilleri et al. 1993). Both take place in the cortical network. Excitatory phenomena are also known from stimulation of the visual system where they are manifested as phosphenes (Barker et al. 1985; Meyer et al. 1991). In our previous work we found that the visual masking effect induced by TMS can be formally described as an elevation in contrast threshold (Kammer and Nusseck 1998). In a second step we combined phosphene documentation and perimetric measurement of visual contrast modulation. In the visual field the contours of

phosphenes and transient scotomas correspond to each other (Kammer 1999). From these observations we postulated that a cortically induced "light," i.e., the phosphene itself, causes the TMS masking effect, which is similar to the masking effect of a light flash.

In most of the previous studies, including our own (Kammer and Nusseck 1998), the occipital pole was stimulated with a simple round coil to obtain significant visual suppression effects. The broad distribution of the induced field produced an uncomfortable side effect, twitches in the subject's neck muscles (Amassian et al. 1989), thereby restricting the number of experimental trials that were possible. Furthermore, psychophysiologically relevant artifacts were induced by facial twitches and eye blinks stemming from the nonfocality of the induced field (Corthout et al. 2000). Recently we developed a stereotactic positioning device that continuously monitors the position of the coil with respect to the position of the head (Kammer et al. 2001). This device made it possible to maintain specified coil positions during a session by giving the subjects visual feedback so that they can correct small head drifts. In addition, measurements at any given coil position may be continued at subsequent sessions since that position can be recreated reliably. Using this technology, we were able to induce a highly reliable masking effect by applying the figure-of-eight coil with a more focal induced field. The figure-of-eight coil produces substantially milder unpleasant side effects than the simple round coil and allows longer investigation sessions with each subject. Thus we now can characterize TMS threshold modulation over a wide range of stimulus onset asynchronies (SOAs) and TMS intensities and estimate the slopes of the psychometric contrast threshold function.

In the present study we characterize the effects of occipital TMS in terms of both psychophysics and functional anatomy. We divide the study into two parts. Here, we report the psychophysical effects of visual suppression. Using a simple visual discrimination paradigm, we measure the contrast modulation effect of TMS in dependence of SOA between visual and magnetic stimulus. In addition to contrast threshold modulation we consider the steepness of the psychometric function (Kontsevich and Tyler 1999; Strasburger 2001; Wichmann and Hill 2001a). In addition, the influence of TMS intensity on masking effects is determined. Previous studies (Beckers and Hömberg 1991; Corthout et al. 2000) suggested that TMS-induced masking depends on TMS intensity and SOA, with an interaction of these two variables. Stronger TMS pulses seem to disrupt visual processing earlier and more effectively. We also characterize the influence of background luminance on the TMS masking effect. An increase in maximum masking time with a decrease in visual stimulus luminance has been observed with TMS (Masur et al. 1993; Miller et al. 1996). On the basis of these observations we discuss the possible electrophysiological mechanisms induced by TMS. We chose biphasic pulses since it is known from the motor system that they are more effective than monophasic pulses (Kammer et al. 2001). In the second part of the study (Kammer et al. 2004) we address the question of brain structures involved in the visual suppression and phosphenes that are induced by TMS. We present the topography of visual masking within the visual field as a function of coil position using perimetry and phosphene drawings. Coil positions are analyzed with respect to the individual functional anatomy of the visual system, measured by functional magnetic resonance imaging. On the basis of these results we discuss the putative structures involved.

Materials and methods

Subjects

Four healthy subjects (aged 21–37 years; two men, two women) including one of the authors (T.K.) participated in the study after giving their written informed consent. None had a history of brain disease; monocular visual acuity (corrected if necessary) was 20/20 or better. All subjects had extensive experience in TMS application and in the psychophysical tasks used. The study was approved by the local internal review board of the Tübingen University Medical Faculty.

Experimental setup

Visual stimuli were presented on a 21-inch monitor (Iiyama Vision Master Pro 21, Kitaowaribe, Japan) controlled by a VSG 2/3 graphics board (Cambridge Research Systems, Rochester, UK) at a frame rate of 100 Hz. The triggers for TMS stimulation were also generated by the VSG graphics board. Subjects sat in a comfortable chair with the heads on a chin rest. They observed the visual stimulus from a distance of 57 cm (contrast thresholds) or 40 cm (perimetry, see below) in an almost completely darkened room.

The Medtronic Dantec Magpro Stimulator (Skovlunde, Denmark) was used in its biphasic mode (maximal rate 0.33 Hz, restricted by the experimental software). The figure-of-eight coil MC-B70 (outer diameter 96 mm) was fixed on a tripod, and the handle was oriented horizontally to the left. Coil position in relation to the head was monitored and registered continuously in all six degrees of freedom—three translational and three rotational—by a custom-made positioning system relative to a head-centered coordinate system (see Kammer et al. 2001). A mechanical digitizing arm (MicroScribe 3DX 6DOF, Immersion, San Jose, Calif., USA) was attached to the subject's head with a headband. A head-based coordinate system was established at the beginning of each session by means of anatomical landmarks. The position of the coil was monitored simultaneously with a second arm. Custom-made software running on a PC continuously calculated the relative position of the coil with respect to the head-based coordinate system.

Prior to the contrast threshold measurements a coil position was determined where a maximal masking effect of TMS was expected. Using a stimulator output intensity of about 80%, the center of the coil was placed at the midline 1–2 cm above the inion, and the coil was moved laterally until the subject perceived a clear phosphene in the contralateral visual field. Then in a test run subjects had to detect the orientation of the visual stimulus (a U-shaped hook, see below) flashed parafoveally within that segment of the visual field where a phosphene appeared. The TMS was triggered 95 ms after the presentation of the visual stimulus, and visual contrast was set slightly above the discrimination threshold under control conditions to test the masking effect of TMS. The coil position was then carefully changed within a range of 2×2 cm until a strong masking effect occurred. This coil position was stored in head-centered coordinates and used for all subsequent masking experiments. To readjust the coil position in a new session the head-based coordinate system was first reestablished. Then the relative distance of the current coil position in all degrees of freedom from the stored position was calculated online and visualized while the investigator carefully moved the tripod together with the coil until the stored position was reached again. Maintenance of the coil position within a session was carefully controlled online by the investigator. If a deviation greater than 1.5 mm or more than 3° in any direction occurred, the experiment in progress was paused. Subjects were given feedback about their own head deviation relative to the chosen coil position by means of two squares displayed on the screen. The square referring to the coil was stationary while the other one displayed the head position relative to the coil position. Translation of the head in the frontal plane translated the square, rotation on a sagittal axis rotated the square, and translation along the sagittal axis shrank or enlarged the square. Rotations on the transversal or axial axis deformed the square into a trapezium to represent the three-dimensional projection of a square rotated in space. With some practice prior to the experiments the subjects were able to readjust their own head position on the basis of the visual feedback. After the readjustment of the head position was finished the paused experiment was resumed.

Contrast threshold measurements

After initiation by the subject with a key press, each trial started with a presentation of the fixation dot of 0.07° for 1 s. Then, in addition to the fixation spot, the target was flashed parafoveally for one frame in the lower left or right quadrant at an angular distance of 0.3° or 0.5° from the fixation spot. The target was a U-shaped hook subtending a visual angle of 0.43° and was composed of a square of 12×12 pixels, from which a rectangle of 4×8 pixels was omitted from one of the four sides to form the symmetric U-shape. Background luminance was either 0.3 or 3 cd/m^2. In a single-interval, four-alternative forced-choice paradigm (4AFC) subjects reported the direction of the opening of the hook by pressing one of four keys (orientation discrimination).

Luminance increment thresholds for orientation discrimination were determined using an adaptive staircase procedure proposed by Kesten (1958; cf. Treutwein 1995). In this procedure the luminance of the stimulus to be presented depends on the preceding responses of the subject as calculated by:

$$L_n = L_{n-1} - \frac{c}{2 + m_{shift}}(R_{n-1} - \Phi) \quad (1)$$

where L_{n-1} and L_n are the luminances of the stimulus in the previous and the current trial, respectively, c is a constant controlling the step size, m_{shift} is the number of reversals so far, R_{n-1} is the response in the previous trial (1 for a correct and 0 for a false response), and Φ is a probability value to which the staircase should converge. To obtain a reasonably robust estimate of the psychometric function's slope as well we intermingled three independent runs with different probability values of 0.4375, 0.625, and 0.8125. These correspond to the probability values 0.25, 0.5, and 0.75 of the psychometric function, corrected for the 4AFC task chance level of 0.25. Each staircase was terminated after five reversals, resulting in about 30–60 stimulus presentations per run.

All raw data measured with the adaptive procedure were used to fit a complete psychometric function. Thresholds and slopes were estimated employing the maximum likelihood fit of the psignifit toolbox version 2.5.4 (Wichmann and Hill 2001a) with a logistic function chosen as model. Confidence intervals (±1 SD) were obtained by the BC_a bootstrap method implemented in psignifit, based on 999 simulations (Wichmann and Hill 2001b). Results are given in target luminance L_{stim} on a logarithmic scale. They can be used to calculate Weber contrast with the formula:

$$C_W = (L_{stim} - L_{back})/L_{back} \quad (2)$$

where L_{back} is the background luminance, here either 0.3 or 3 cd/m^2.

As the main independent parameter, SOA of TMS was varied. In a first approach, SOAs ranging from +5 to +155 ms were investigated in each subject in steps of 10 ms. The range was extended up to SOAs between −125 and +205 ms until the luminance increment result reached the level of the control measurement in the absence of TMS, to capture the complete TMS modulation range. Note that the SOA was measured from the actual onset of the visual stimulus in the middle of the screen, not from the onset of the frame sync signal at which time the beam starts out invisibly at the upper left corner of the screen. Negative values indicate that the TMS was triggered prior to the visual stimulus and positive values that it occurred after presentation of the visual stimulus. The second independent parameter was background luminance, either

0.3 or 3 cd/m^2. The third independent parameter was TMS intensity, presented as a percentage of the maximal output energy of 300 J (Kammer et al. 2001). With the background luminance of 0.3 cd/m^2, at least three different intensities were investigated in steps of 10%.

Perimetry

Topography of contrast threshold modulation in the visual field of the right eye was measured using a static-perimetry approach following the strategy of the Tübingen Automatic Perimeter (Dorner-Schandl et al. 1993; see Kammer 1999). Subjects reported the presence of a 0.5°×0.5° square that was flashed for one frame after a 1000-ms fixation period by pressing a button ("yes/no" response). The square randomly appeared at one of 32 positions arranged in three circles around the fixation spot (0.1°×0.1°) at an eccentricity of 1°, 4°, or 10° (see Fig. 4). For each of the 32 positions the detection threshold was determined using a simple one-up/one-down staircase procedure. Luminance of the square for its first presentation was set to be suprathreshold. Each staircase was terminated after two reversals, and threshold for the given position was calculated as the mean luminance at the two reversals. To check for false alarms 10% of the trials were catch trials without any visible target. Maintenance of fixation was monitored by additionally presenting a 33rd spot located in the blind spot of the subject that had been individually determined in a control run. Only runs with no positive response to the catch trials or to the 33rd spot were accepted. Fewer than 5% of the runs were discarded.

Target luminance was converted to dB by:

$$S(\mathrm{dB}) = 10 * \log_{10}(L_{max}/(L_{test} - L_{back})) \quad (3)$$

with S: light-difference sensitivity, L_{max}: maximum luminance of the screen (110 cd/m^2), and L_{test}, L_{back}: test and background luminance. Note that this definition, which is commonly used in perimetry, has a simple inverse relationship with Weber contrast (2), given by:

$$S(\mathrm{dB}) = -10 * \log_{10} C_w + \mathrm{c} \quad (4)$$

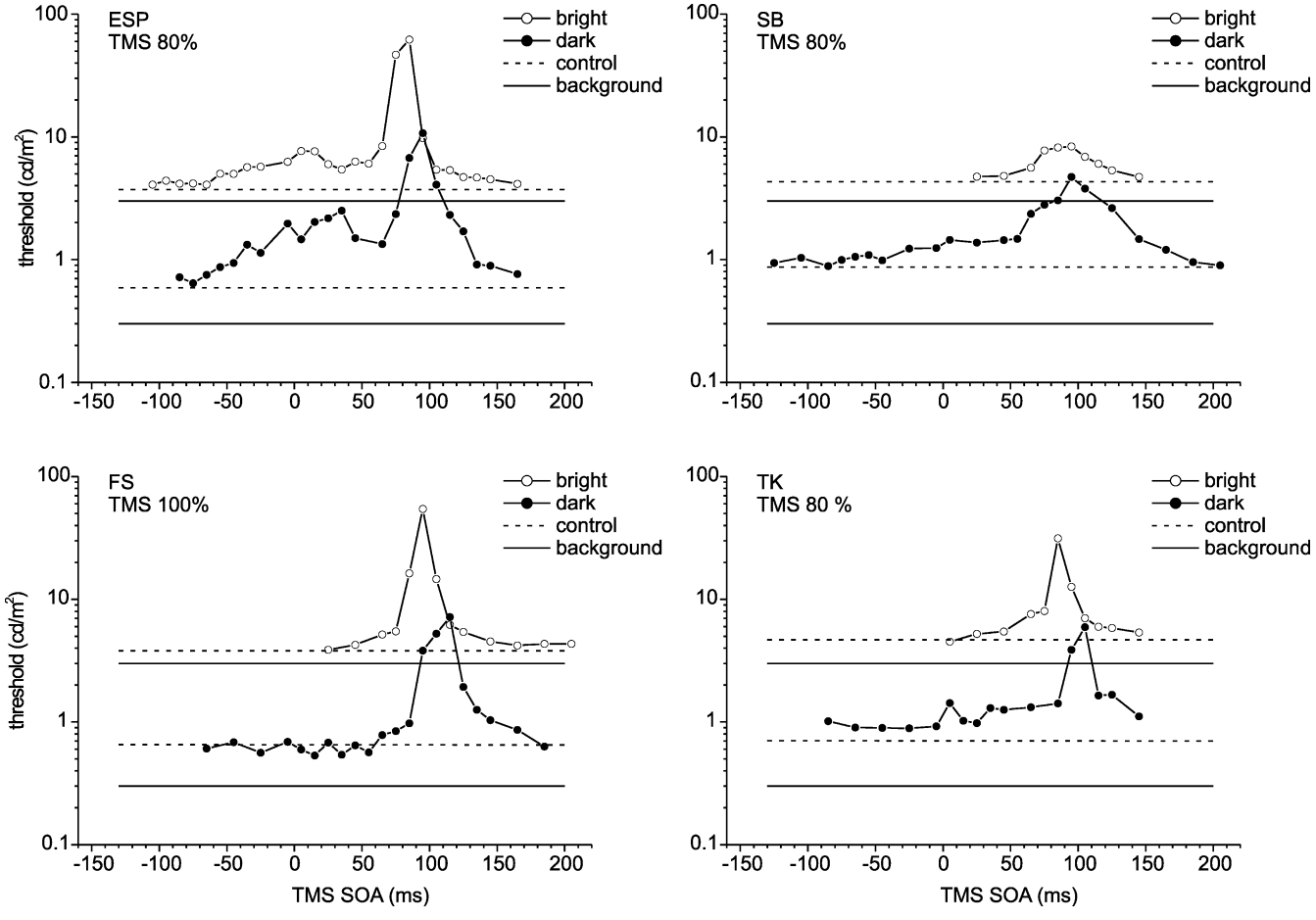

Fig. 1 Modulation of contrast threshold as a function of TMS SOA (*abscissa*) and background luminance (*ordinate*; note log style) in four subjects. *Lines* Background levels 0.3 cd/m^2 (*dark*) and 3 cd/m^2 (*bright*); *stippled lines* contrast thresholds in the absence of TMS as control values; *open circles* measurements with bright background; *filled circles* measurements with dark background. Polar coordinates of the center of the flashed visual object (rotation, distance in degrees): *ESP*, 225°, 0.5° (*lower left*); *SB*, 225°, 0.3°; *FS*, 315°, 0.5 (*lower right*); *TK*, 315°, 0.5

where c is a constant, and $c=10\ log_{10}\ (L_{max}-L_{back})$.

The detection threshold at each visual field position was determined by a simple staircase procedure, as follows (Dorner-Schandl et al. 1993). Luminance of the first presentation at a given position was adjusted to be just suprathreshold under control conditions. In the case of a "yes" response, luminance for the next target presentation was reduced, and in the case of a 'no' response luminance was increased, both in steps of 1 dB. The threshold at each position was determined after two reversals by calculating their mean luminance level. To shorten the threshold procedure in case of a 'no' answer at the very first presentation, the next luminance presented there was 0 dB (maximal intensity of the screen), as implemented in the Tübinger Automatic Perimeter. If the subject then responded 'yes', the next luminance presented there was half of thedB value at the first presentation. In case of two consecutive 'no' answers at 0 dB, the staircase procedure was terminated. Luminance thresholds were always determined pairwise without and with TMS, and changes in thresholds were plotted using a gray scale where no change was white and an elevation of contrast threshold above 16 dB was black (compare Fig. 4).

Results

In all subjects TMS within a critical time window induced a pronounced elevation of contrast threshold by a factor ranging 5 to 28 (see Figs. 1, 2, 3). In addition to the contrast threshold elevation each magnetic stimulus evoked a phosphene. The emergence of the phosphene depended on the attention of the subject. While concentrating on the detection of visual stimuli phosphenes appeared to be less vivid or even completely absent. However, on request they were always observed immediately. A detailed description of phosphene phenomenology evoked at the same stimulation sites chosen here for visual suppression is given in the companion paper (Kammer et al. 2004).

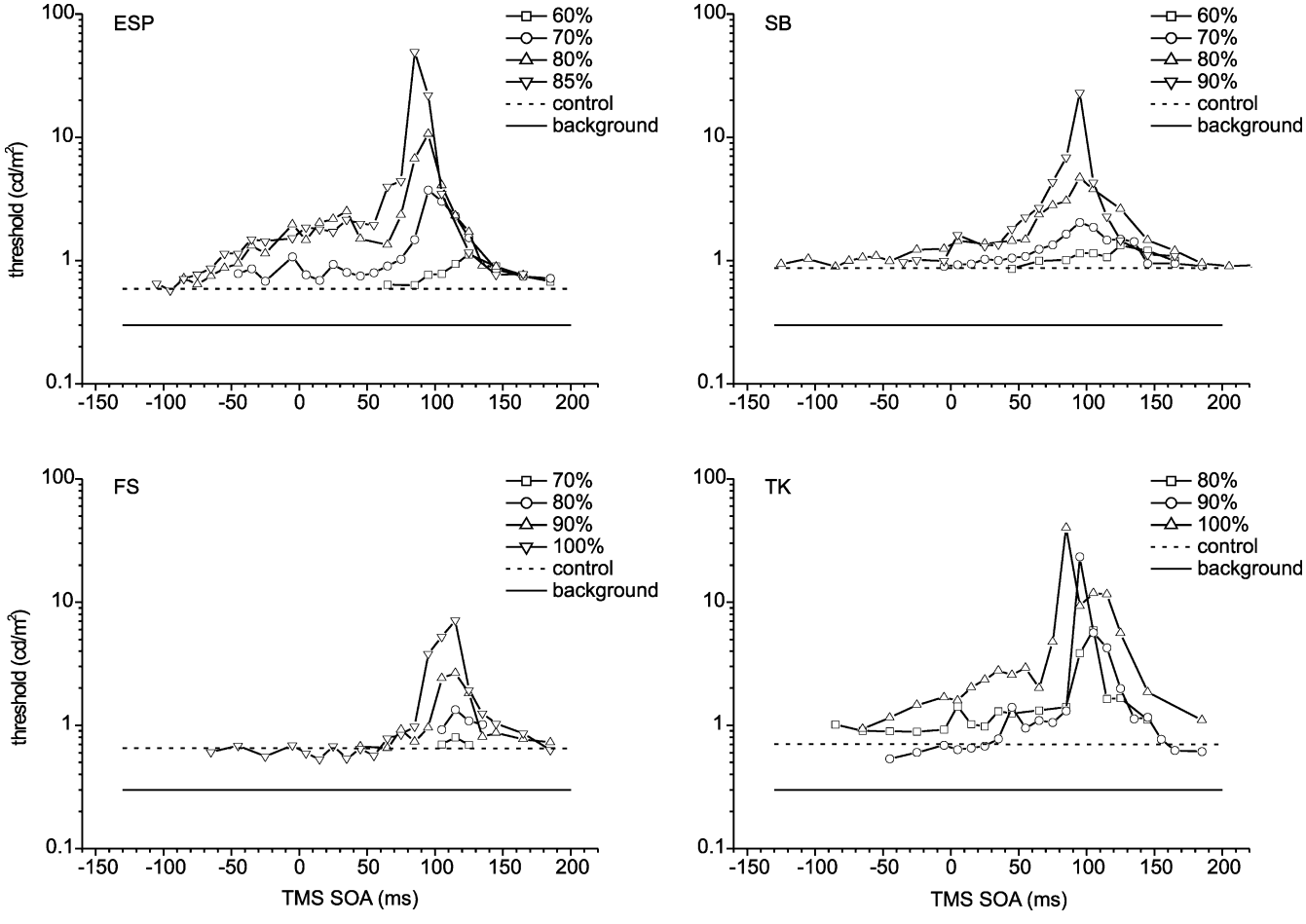

Fig. 2 Effect of TMS intensity on contrast threshold modulation in four subjects. Background luminance was 0.3 cd/m^2 (*horizontal line*). *Stippled lines* Control values of contrast threshold without masking. The TMS intensities (given as percentage of maximal output) are shown with different symbols. Note that the range of TMS intensities was suitably chosen for each subject and therefore differs between subjects

Effect of background luminance

The effect of the adaptation level on TMS threshold modulation was investigated using two different values for the background luminance, 0.3 and 3 cd/m^2. For both levels we found a bell-shaped threshold elevation as a function of the SOA (Fig. 1). The maximum relative threshold elevation was roughly the same for the two adaptation levels but was shifted to earlier SOAs with the higher background luminance. In the mean the maximum occurred at +101.9 ms SOA (range 93–110 ms) with low background level and at +87.9 ms SOA (range 81–95 ms) with the high background level.

Effect of TMS intensity

The effect of increasing TMS intensity on threshold modulation is shown in Fig. 2. With increasingly stronger TMS pulses the magnitude of the threshold elevation increased. In addition, the SOA time for the maximum effect decreased, resulting in a leftward shift of the curves. Furthermore, with higher TMS intensities the curves became asymmetric, with threshold elevations at lower SOA values between −50 ms and +50 ms in three of the four subjects.

To determine whether this early threshold elevation stemmed from cortical processes or was caused by a nonspecific (noncortical) side effect of TMS we performed static perimetry in one of our subjects (ESP). Modulation of detection threshold by TMS was measured for 32 light spots in a visual field of 10° radius (the distribution shown as black dots in Fig. 3 left) and compared with the respective control measurements at two representative SOAs (Fig. 3). Changes caused by TMS are depicted using a gray scale, where white indicates no change and black an elevation in detection threshold of 16 dB or more. At an SOA of +95 ms thresholds were elevated in a segment in the lower left quadrant of the visual field (right panel). A weaker threshold modulation with a similar topography in the visual field was observed at an SOA of +25 ms (left panel).

To quantify the relationship between TMS intensity and threshold modulation Gaussian fits were applied to the data in Fig. 2 (not shown). The interrelationships between the parameters at the maxima of these fits are shown in Fig. 4. Increasing TMS intensity results in a systematic decrease in the SOA for the maximal modulatory effect (peak SOA, Fig. 4a) and an increase in the maximal contrast threshold elevation (peak threshold, Fig. 4b). The relationship between threshold modulation (log scale) and peak SOA in turn is shown in Fig. 4c. As peak threshold increases, peak SOA decreases. An exponential decay function was fitted to the values yielding an SOA_0 of +72.06 ms for the lower asymptote to which the function is converging. In addition to the values measured at a background luminance of 0.3 cd/m^2 (filled symbols), Fig. 4c also includes the four peak values stemming from a background of 3 cd/m^2 (Fig. 1, open symbols).

Steepness of psychometric functions

Reliable slope estimation is generally difficult in the absence of a sufficiently large number of trials per psychometric function (Wichmann and Hill 2001a). Using the psignifit toolbox without constraints on the maximum-likelihood fit we found a broad distribution of slope values even in the control measurements without TMS, ranging from 0.74 up to 1892. With TMS masking the distribution of slope values was substantially larger, ranging from 0.06 up to 5180. The highest values (>100) occurred independently of the SOA and were due to insufficient raw data (not shown). Figure 5a presents the

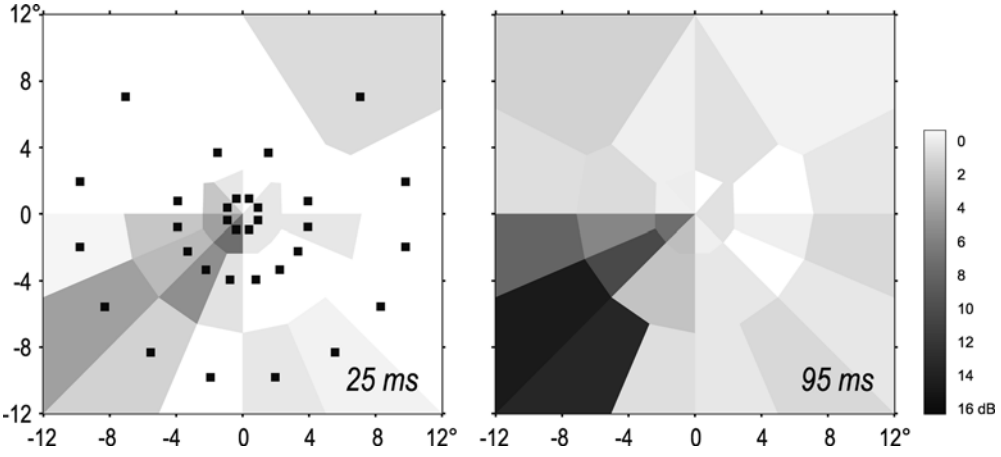

Fig. 3 Topography of threshold modulation in the visual field with two different SOAs (left +25 ms, right +95 ms), measured by static perimetry in subject *ESP*. The mosaic of gray fields indicates the amount of threshold elevation in comparison to a control measurement in the absence of TMS (transient relative scotoma). Each mosaic area represents the threshold value measured with a small light spot. The angular position in the visual field of the spots is shown in the left panel. In the two outer circlets the density of spots is higher in the lower quadrants since threshold modulation was expected mainly in the lower visual field. The amount of threshold elevation is coded from white to black (0–16 dB; *right*). Maximal threshold modulations were: TMS SOA +25 ms, 7 dB (1.74 cd/m^2); TMS SOA +95 ms, 13 dB (11.7 cd/m^2)

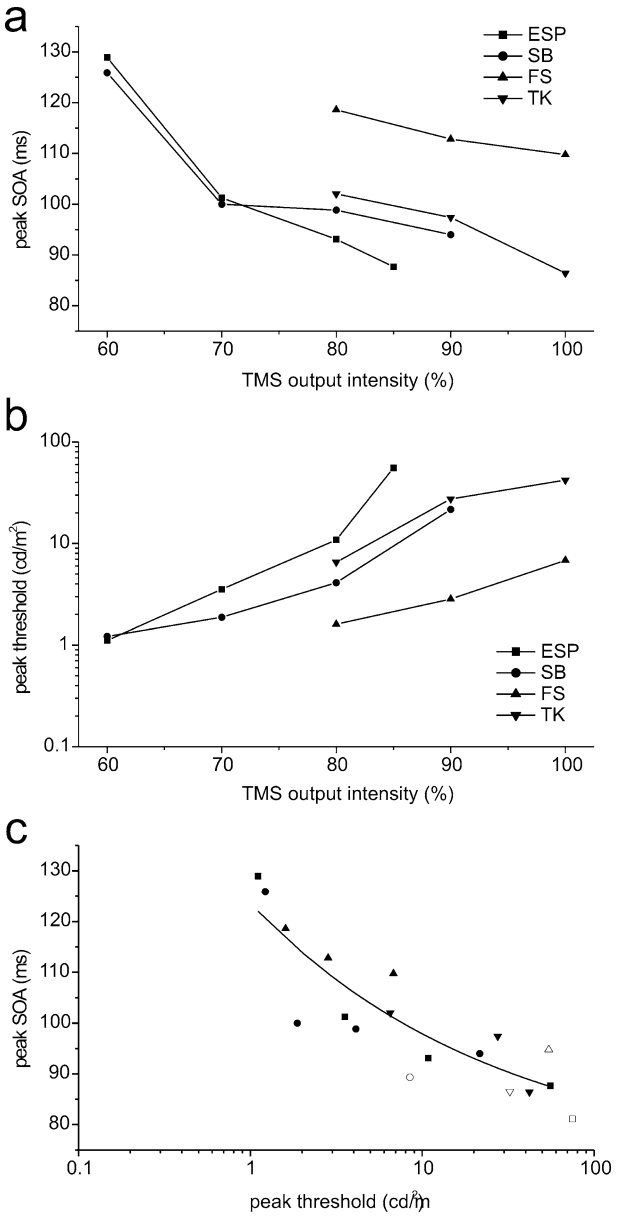

Fig. 4 Dependence of threshold modulation effects on TMS intensity. **a** Peak stimulus onset asynchrony (SOA) of the maximum modulation effect. **b** Peak threshold elevation. **c** Correlation of SOA and peak threshold elevation. Peak values were calculated using Gaussian fits applied to the data shown in Fig. 2 (fits not shown). Different symbols code for different subjects. **a**, **b** Only values measured at a background luminance of 0.3 cd/m^2 are shown (*filled symbols*). **c** Measurements with a background luminance of 3 cd/m^2 are also incorporated (*open symbols*). The exponential function was fitted to the filled symbols only. The function follows Steven's power law in the form $SOA=SOA_0 + \alpha L^{\beta}$, where L is the luminance, SOA_0 is the asymptotic value SOA approaches with increasing L, and α and β are fitting parameters. With a fixed β of −0.3 (Kammer et al. 1999), SOA_0 is +72.06 ms and α 51.53 (χ^2=44.36, R^2=0.77)

geometric mean values of slopes across the four subjects in the range of TMS SOA from −65 ms to +145 ms. Measurements with the two highest TMS intensity values for each subject are included (see Fig. 2). Most of the averaged slope values were below the control value, which is given as a horizontal stippled line. The most prominent decrease in slope occurs within the critical time window of +75 to +115 ms. To obtain a robust estimate of the slopes raw data were pooled across subjects and conditions after normalizing luminances to the individual thresholds (Strasburger 2001). Figure 5b presents three psychometric functions estimated after pooling. The slopes of all control measurements in the absence of TMS was 2.08 (1.98–2.18), decreasing to 1.59 (1.46–1.74, all subjects, the two highest TMS intensities included, TMS SOA from −65 ms to +5 ms) and to 0.95 (0.89–1.07, TMS SOA from +75 ms to +115 ms). These decreases were significantly different from each other and from the control value as indicated by the confidence intervals (±1 SD) given in brackets. In control experiments the masking effect of a light flash on the orientation discrimination task was investigated (four subjects, data not shown). Contrast thresholds were elevated with SOAs from −35 ms to + 25 ms in a range comparable to the TMS effects. The slope of the psychometric function estimated after pooling these flash data was found to be 2.28 (2.05–2.47). This slight increase was not significant in comparison to the control value of 2.08 (1.98–2.18).

Discussion

The main findings of the present study are: (a) The suppression effect of TMS on visual perception can be reliably determined as contrast threshold elevation using a focal coil in combination with a stereotactic positioning device. (b) Contrast threshold is modulated in dependence on TMS SOA in a bell-shaped manner, with a maximum at about +100 ms (TMS after visual stimulus). The maximum SOA decays exponentially with adaptation to higher background luminance and with higher TMS intensities, yielding larger threshold elevations. (c) Masking with TMS decreases the slope of the psychometric function by a factor of about 2. (d) Higher TMS intensities even raise contrast thresholds with shorter SOAs, resulting in an asymmetric deformation of the bell-shaped modulation function. Static perimetry excludes an unspecific mechanism for shorter SOAs but proves a retinotopic contrast elevation in the same segment of the visual field as that seen with maximum SOA.

Comparison of contrast threshold measurement and the percent correct method

The classical psychophysical approach to measuring the visual suppression effect introduced by Amassian et al. (1989) presents visual stimuli with a fixed luminance level (Amassian et al. 1993; Beckers and Hömberg 1991; Beckers and Zeki 1995; Corthout et al. 1999a, 1999b, 2000; Hotson et al. 1994; Masur et al. 1993; Miller et al. 1996). With TMS SOA as the independent variable the dependent variable becomes the proportion of correct responses. Our strategy for determining contrast thresholds (Kammer and Nusseck 1998; see also Paulus et al. 1999)

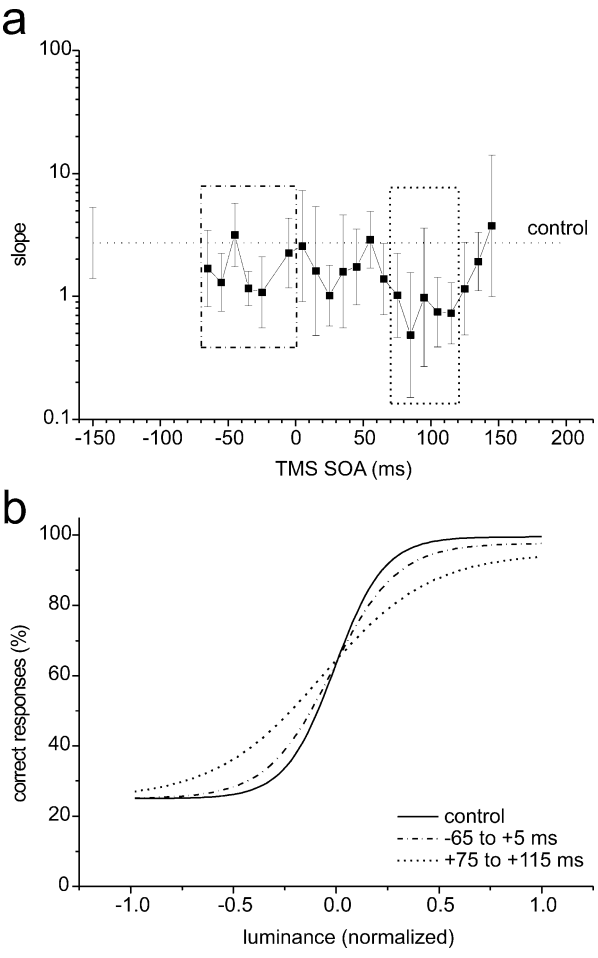

Fig. 5 Slopes of estimated threshold functions in dependence on SOA. **a** Slopes from the TMS threshold measurements given in Fig. 2 (background luminance 0.3 cd/m^2) are shown as geometric means (±SD) averaged over the four subjects. The two measurements with the highest TMS intensity values were pooled together. The geometric mean of slope for all control measurements in the absence of TMS is shown as a horizontal stippled line (error bars at −150 ms SOA). *Stippled squares* Conditions that were further pooled. **b** Psychometric functions of TMS masking estimated from pooled data. Raw data from each measurement were normalized to the estimated threshold before pooling. Three data sets were created: all control measurements in the absence of TMS, all measurements with a TMS SOA from −65 ms to +5 ms, and all measurements with a TMS SOA of +75 ms to +115 ms. For both TMS sets the two highest stimulator output intensities applied were chosen. For slope values and confidence intervals, see text. Due to the normalization threshold luminance for all functions is zero

can be seen as an inversion of the previous method, in which the two criterion variables, contrast and proportion correct, are linked by the psychometric function. Whereas correct responses in dependence of TMS SOA result in an inverted bell-shaped function (Amassian et al. 1989), our approach to measuring contrast thresholds yields an upright bell-shaped function. Since the psychometric function is steeper at the threshold than at any other point, measuring thresholds instead of proportion of correct responses always yields a more sensitive measure of the effect in question.

A related effect and difference between the methods is that the correct-response criterion commonly used until now has a fixed test range strongly dependent on the settings of the task (contrast and duration of the visual stimulus). It therefore often shows ceiling or floor effects whereas the measurement of contrast thresholds always yields a quantitative result. A disadvantage of course is that the required number of observations for measuring a threshold is larger than that needed to determine the proportion of correct responses at some fixed stimulus setting. For the present data we used an adaptive staircase procedure with three independent staircases running interleaved with about 50 observations per run, yielding a robust estimate of contrast thresholds.

The increased number of observations allows parametric results of the TMS SOA modulation function to be calculated. We thus believe that masking effects of TMS can be more precisely described by threshold measurements than by a proportion-correct criterion.

Slopes

To estimate the slope of the contrast psychometric function we adjusted the staircases to converge at three different points of the function (King-Smith and Rose 1997). The number of observations (30–60) proved, however, somewhat small to obtain a clear result for the modulation of the slope in individual subjects. As pointed out previously (Kontsevich and Tyler 1999; Wichmann and Hill 2001a), at least 300 observations are required for slope estimation. In our measurements (Fig. 5) slopes were broadly distributed, with a few outliers, such extremely high values resulting from a flat maximum-likelihood surface and/or unlucky sampling of the psychometric function. To a critical degree slope estimation depends on the proper placement of trials (Wichmann and Hill 2001a) and is sensitive to unlikely responses when the number of trials is low, giving rise to large variance of the slope estimate even though the process characteristic is constant (Treutwein and Strasburger 1999). Therefore to achieve a sufficient number of trials to estimate the overall effect of TMS on psychometric function slope we pooled data across subjects and SOA times, using both standard parametric slope averaging (Fig. 5a) and pooling after normalization of the raw data to the estimated thresholds (Fig. 5b; Strasburger 2001). Both methods show a reduction in slope by a factor of about two with TMS masking at SOAs approx. +100 ms. This may indicate that, in terms of signal detection theory, TMS not only shifts the mean of the internal noise distribution towards higher values (increasing threshold) but in addition increases the variance of internal noise in the system (shallower psychometric functions). It is tempting to speculate that TMS interrupts some but not all neuronal signal transmitting fibers or synapses such that redundancy is reduced and thus reliability of transmission is decreased. Behaviorally this decreases the reliability of the subjects' responses above threshold. In contrast to the TMS effect

on slopes no significant change in slope was found with masking by light (data not shown), indicating that the variance of internal noise is not modulated by that kind of masking.

Relationship between threshold modulation, luminance of the stimuli, adaptation level, and TMS intensity

Increasing the luminance of the visual stimulus decreases the TMS SOA that yields the maximum masking effect (Figs. 1, 2, and 4). This relationship probably reflects the dependence of the retinocortical transmission time on the luminance of the visual stimulus (Kammer et al. 1999; Maunsell and Gibson 1992), the latter depending mainly on retinal latencies (Bolz et al. 1982; Lennie 1981). The TMS SOA shift has previously been demonstrated by Masur et al. (1993) and by Miller et al. (1996) using the percent-correct method. With the more sensitive and reliable contrast-threshold measure we could calculate peak SOA for maximal TMS effects for the individual subject, whereas in previous approaches (Miller et al. 1996) only the group mean could be used.

The decrease in maximum masking time with increasing threshold luminances appears to follow the same kind of exponential decay function $t=t_0+\alpha L^{\beta}$ that is known for simple reaction times (e.g., Mansfield 1973) and for the components of visual evoked potentials (VEPs; Jaskowski et al. 1990; Kammer et al. 1999; Osaka and Yamamoto 1978; Vaughan et al. 1966). A comparison of the asymptotic value SOA_0 from the present study (72 ms) with VEP and RT parameters in (Kammer et al. 1999) seems to indicate that the TMS suppression process occurs between the VEP components N80 (t_0 65 ms) and P100 (t_0 87 ms). However, in the present study the factor α is somewhat higher (51.5) than the values in the previous study (α from 22 to 44), probably due to major differences in visual stimulation such as background luminance or size of the visual stimulus. A direct comparison of VEP and TMS suppression effect is required to clarify the functional relationship between suppression effect and components of the VEP.

We observed a decrease in maximum masking time with two different manipulations: either with an increase in background adaptation level of one order of magnitude from 0.3 to 3 cd/m^2 (Fig. 1) or with an increase in TMS intensity yielding a more pronounced contrast threshold elevation (Fig. 2). Both manipulations required higher luminances of the visual target to overcome the masking effect of TMS at the critical SOA and as a result speeded up the maximum masking time. Since we did not vary TMS intensity at the higher background adaptation level we cannot fully describe the interaction of the two parameters on the maximum masking time. The values stemming from higher background adaptation seem to have a tendency to be shifted to a lower SOA_0 (Fig. 4c, open symbols), suggesting that the masking times can be speeded up with higher background luminance. Further investigations with a larger range of background luminances down to complete dark adaptation would be required to clarify this issue.

Deformation of the bell-shaped function with higher TMS intensities

Suppression effects of TMS in a time window below +80 ms SOA have been reported. With increasing TMS intensity, Beckers and Hömberg (1991) observed maximal visual suppression even at +40 ms SOA in the group data and described suppression in a single subject even with negative SOA (the TMS pulse occurring before the visual stimulus). They postulated that increasing TMS intensity results in a longer lasting suppression effect. Assuming a fixed critical time window for the interaction of the visual processing and the TMS pulse, higher TMS intensities then modulate the perception even with shorter SOAs. Corthout et al. (1999a, 1999b) reinvestigated this phenomenon and observed TMS suppression effects in several time windows before and after the onset of the visual stimulus. They demonstrated that TMS-evoked eye blinks induce the visual suppression in the earliest time window with a maximum at −70 ms SOA ("dip 0"). A second period at the time of presenting the visual stimulus was observed between −20 ms and +40 ms SOA ("dip 1"). This suppression time window was clearly separated from the classical suppression window located at +110 ms SOA ("dip 2"). The authors attributed the suppression effects of their "dip 1" to an early cortical signal reaching V1 within 20–40 ms. They speculated that the classical suppression period reflects either stimulation of extrastriate areas or a second vulnerable cortical process in V1 after the visual signal has passed a reentry loop. In a follow-up study (Corthout et al. 2000) the authors found that with increasing TMS intensity the early time window was enlarged and fused with induced blink artifacts.

Our results (Fig. 2) confirm that with higher TMS intensities suppression effects occur even with shorter SOA (Beckers and Hömberg 1991; Corthout et al. 2000). In contrast to Corthout et al. (1999a), we did not observe clearly separable time windows for suppression but rather a continuity of SOAs causing threshold elevation in three of our four subjects. The masking effect with short SOA increased with higher TMS intensities, similar to the maximum masking effect at approx. +100 ms SOA. In subject FS we did not observe short SOA effects since we reached the maximum stimulation power even with only moderate elevation effects (Fig. 2). We can exclude an unspecific TMS side effect for the short SOA suppression. The perimetric test in one subject (Fig. 3) revealed that similar to SOAs around + 100 ms for the suppression with short SOA a subcortical or cortical process in a retinotopic area of the visual pathway is responsible since the same segmental pattern within the visual field was found as with longer SOAs. An unspecific TMS side effect would have been expected to cause a nonfocal threshold elevation distributed over a large part or the whole of the visual

field. Some discrepancies between our findings and those reported by Corthout et al. (1999a) might be caused by differences in methodology, namely the geometry of the TMS coil. Whereas Corthout et al. (1999a) used a round coil, we employed a figure-of-eight coil, yielding a better focused magnetic field. This might explain why we did not observe effects before −70 ms SOA that could be attributed to blink artifacts. The nonfocality might account for the differences observed in the time window around visual stimulus presentation, since the round coil is expected to reach cortical and subcortical structures at larger distances from the coil.

Possible electrophysiological mechanisms

TMS applied to the cortex induces both excitation and inhibition, as demonstrated in the human motor system (Hallett 2000). Concerning the contrast threshold effect in the visual system an elegant and simple explanation for the underlying electrophysiological mechanism would be the competition of two types of excitation, namely the visual stimulus and the TMS induced excitation, which results in the perception of a phosphene in addition to its masking effect (see Kammer 1999). However, the data presented here are no longer suggestive of this hypothesis but are consistent with an inhibitory mechanism in the network, as proposed by Amassian et al. (1989), for the following two reasons. (a) The threshold modulation effect of stronger TMS pulses lasts longer in the system causing the deformation of the bell-shaped function (Fig. 2). This intensity dependence parallels the positive correlation of silent period duration and TMS intensity in the motor system (Fuhr et al. 1991; Inghilleri et al. 1993). (b) The stimulation intensity required to induce phosphenes is by about 59% lower than the intensity causing threshold modulation (Table 1 in the companion contribution, Kammer et al. 2004). One would expect reasonably similar thresholds for both phosphenes and masking effect if the latter is based on excitation.

Recently the first successful single cell recordings of TMS evoked activity from cats visual cortex were presented by Moliadze et al. (2003). They demonstrate that TMS evokes a complex pattern of excitation and inhibition lasting up to 5 s that depends on stimulus intensity. In the time window of 200 ms after TMS they observed a facilitation with weak magnetic stimuli. However, stronger stimuli evoked a facilitation interrupted by an early inhibition at 100–200 ms. One might speculate that this pattern could explain our findings: lower TMS intensity might act by excitation directly in the critical time window whereas higher intensities might act inhibitory when applied before the critical time window.

The coexistence of phosphenes and visual suppression is investigated with respect to the cortical stimulation site in the companion contribution (Kammer et al. 2004) and a more detailed discussion on the involved structures is presented there.

Acknowledgements We thank Sandra Beck, Kuno Kirschfeld, and Hans-Günther Nusseck for support and for many fruitful discussions.

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