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Changes in Visual Responses in the Feline dLGN: Selective Thalamic Suppression Induced by Transcranial Magnetic Stimulation of V1

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Abstract. Transcranial magnetic stimulation (TMS) of the cortex can modify activity noninvasively and produce either excitatory or inhibitory effects, depending on stimulus parameters. Here we demonstrate controlled inhibitory effects on the large corticogeniculate feedback pathway from primary visual cortex to cells of the dorsal lateral geniculate nucleus (dLGN) that are focal and reversible—induced by either single pulses or trains of pulses of TMS. These effects selectively suppress the sustained component of responses to flashed spots or moving grating stimuli and are the result of loss of spikes fired in tonic mode, whereas the number of spikes fired in bursts remain the same. We conclude that acute inactivation of the corticogeniculate downflow selectively affects the tonic mode. We found no evidence to suggest that cortical inactivation increased burst frequency.

Key words. Burst, Corticothalamic, TMS

Introduction

The dorsal lateral geniculate nucleus (dLGN) receives extensive feedback originating in layer 6 of the visual cortex, and although this input largely exceeds the number of retinal fibers (Van Horn and others 2000), its physiological role is still unclear. Early experiments in which the corticofugal projection was inactivated suggested a broad, nonspecific facilitatory action from the cortex onto the dLGN (Kalil and Chase 1970; Singer 1977). It was later found that the corticothalamic feedback influences the spatial and temporal structure of dLGN receptive fields (RFs) (Tsumoto and others 1978; Vidyasagar and Urbas 1982; McClurkin and Marrocco 1984; Murphy and Sillito 1987; Sillito and others 1993, 1994; Cudeiro and Sillito 1996; Wörgötter and others 1998; Cudeiro and others 2000) and increases the spatial resolution of thalamocortical inputs by sharpening thalamic RF focus (Murphy and Sillito 1987; Rivadulla and others 2002; Sillito and Jones 2002). In addition, the corticofugal pathway has been suggested to be involved in the state-dependent control of the general responsiveness of thalamic relay cells (Funke and Eysel 1992; Wörgötter and others 1998). Most recently, it has been implicated in the control of the burst/tonic response modes of dLGN cells (Godwin, Vaughan, and Sherman 1996; reviewed in Sherman 2001a). It has been suggested that spikes fired in bursts, while relatively few in number, paradoxically provide a significant source of cortical arousal, even in the awake animal, which, in turn, shifts lateral geniculate nucleus (LGN) cells from burst to tonic mode firing (Guido and Weyand 1995; Ramcharan and others 2000; Sherman 2001b). However, the anesthetized cat model has been widely used to probe this function (Guido and others 1992, 1995; Rivadulla and others 2003; Alitto and others 2005).

The majority of the experiments where cortical recovery can be obtained following intervention (chemical inactivation, cooling, etc.) have a long time constant in the scale of minutes to hours. However, it is known that spatiotemporal (or dynamic) RF properties of neurons in the visual system change as a function of poststimulus time in the order of milliseconds (e.g., see Ringach and others 1997), and several computational models have also suggested that feedback circuitry may underlie the time-varying properties of cortical and thalamic neurons in many sensory systems (for a review, see Ghazanfar and others 2001). We have therefore sought for a tool that would allow us to study the function of the visual corticothalamic feedback over a wide temporal range, from the subsecond up to periods of minutes, but both in a reliable and reproducible way. We have chosen to use repetitive transcranial magnetic stimulation (rTMS) to disrupt visual cortex activity across the timescale we believe to be important to the

relationship between cortex and thalamus. Intensity and frequency appear to determine if rTMS is excitatory (10 Hz and above) or depressive (~1 to 6 Hz) (Kujirai and others 1993; Pascual-Leone and others 1993, 1994; Wassermann and others 1996; Berardelli and others 1998; Gangitano and others 2002). Using the appropriate parameters, rTMS can transiently suppress visual perception (Amassian and others 1989; Maccabee and others 1991; Beckers and Zeki 1995).

Our data provide new and robust evidence on the function of the corticothalamic feedback in the visual system compatible with the role of a cortical modulation of thalamic activity. The rTMS used here to inactivate the corticothalamic pathway yielded focal reversible effects that selectively interfere with the tonic but not the burst response mode in dLGN cells.

Materials and methods

Four adult cats of either sex were prepared following standard procedures used in our laboratory for experiments involving extracellular recordings along the visual pathway (Rivadulla and others 2002, 2003). Briefly, animals were anesthetized with halothane (5% for induction, 1.5–2% for surgery, and 0.1–1% for maintenance) in nitrous oxide (70%) and oxygen (30%). The trachea was cannulated, an intravenously (i.v.) line inserted, and appropriate craniotomies performed for both cortical and thalamic recordings. To prevent eye movements, animals were paralyzed with gallamine triethiodide (loading dose of 40 mg, maintenance 10 mg/kg/h i.v.) and held in a stereotaxic frame. End-tidal CO_2 levels, electrocardiogram waveform and intersystolic interval, and the frequency of spindles in the electroencephalography (EEG) were monitored continuously throughout the experiment. The rate and depth of artificial respiration was adjusted to maintain end-tidal CO_2 at 3.8–4.2%; the level of halothane was chosen to achieve a state of light anesthesia. Once a stable state was reached, any variations in the monitored parameters (change in the frequency of spindles, fall or fluctuation in the intersystolic interval, and rise in end-tidal CO_2) commensurate with a change in the depth of anesthesia were compensated for by alterations in the level of halothane. Management of anesthesia was based upon spectrum of measures and is in keeping with the guidelines given by the UK Home Office. Wound margins were treated with lidocaine hydrochloride administered subcutaneously. Ear bars of the stereotaxic frame were coated with lidocaine gel. The eyes were treated with atropine methonitrate and phenylephrine hydrochloride, protected with zero-power contact lenses, and brought to focus on a semiopaque tangent screen 57 cm distant using appropriate trial-case lenses. Visual stimuli were viewed monocularly through 3-mm artificial pupils. To further reduce possible eye movement artifacts, rigid posts were fixed to the sclera and attached to the stereotaxic frame. At the end of the experiment the animal was killed by anesthetic overdose and, where required, tissue taken for histological examination. The procedures conformed to the Spanish Physiology Society and the International Council for Laboratory Animal Science and the European Union (statute nr 86/809).

Data Acquisition and Analysis

Computer-controlled visual stimuli comprised sinusoidal drifting wave gratings and flashing spots of different diameters (Lohmann Research Equipment, Castrop-Rauxel, Germany), which were presented on a computer monitor with a mean luminance of 14 cd/m^2 at a contrast of 0.6 and refresh rate 128 Hz.

Magnetic Stimulation

The rTMS was carried out with a MagStim Rapid system (The MagStim Company Ltd, Whitland, UK) equipped with 2 boosters and applied to the occipital cortex of cats via a figure-of-eight coil (2 × 25 mm). The midpoint of the coil was centered over the interhemispheric cranial suture at the level of area 17 (Horsley-Clarke antero-posterior [AP] 0 to −6, Medio-lateral [ML] 0) directly touching the exposed bone. The coil was fixed by a mechanical arm at an angle of about 60° (wings located laterally) with the handle pointing up and backwards (see Fig. 1*A*, left). In terms of stimulation frequency, we utilized 2 different protocols (see Fig. 1*A*): 1) 1 Hz, that is, one pulse per second; this protocol was utilized with the flashing spot paradigm, varying the time interval between transcranial magnetic stimulation (TMS) (see below) and visual stimulation (total number of stimulus pulses/run ranged from 40 to 60) and 2) modified rTMS, in which we administered repeated 6-Hz pulses of 1-s duration, at a frequency of 0.1 Hz, that is, a train of 6 pulses in 1 s (6 Hz), repeated every 10 s (0.1-Hz intertrain interval). The total number of trains administered then varied between 6 and 8 (note that for evaluation of TMS effect on spontaneous activity, the number of trains increased to 30), according to the number of trials recorded, with the total number of pulses administered ranging from 36 to 48 per run. We refer to this as the 6@0.1 Hz protocol.

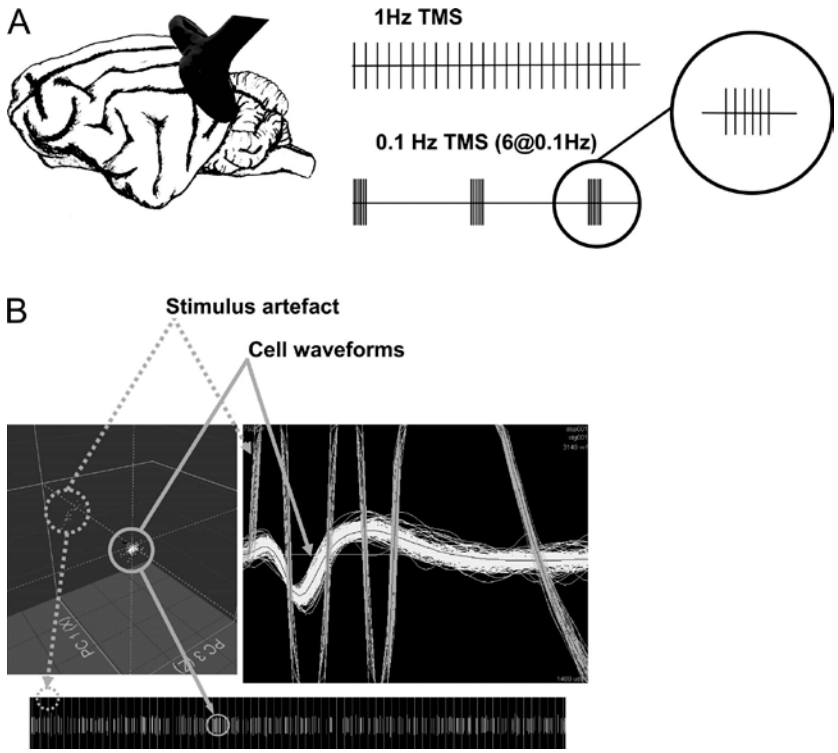

Figure 1. Diagrammatic representation of the methods employed. (*A*) Cartoon of the approximate position and orientation of the "figure-of-eight" TMS coil, placed directly in contact with the exposed skull of the animal—craniotomies were performed only for the insertion of electrodes. The right side illustrates the 2 rTMS paradigms—1-Hz or single stimulus pulses (above) and our "6@0.1 Hz" rTMS. (*B*) During longer recording periods, it was necessary to remove the stimulus artifact from the spike-counting process—here we illustrate the software approach to analyze spike events as clusters and the clear separation of the neuron and the artifact. During our rTMS, the very short duration of the stimuli caused only minor loss of spiking events (lower illustration).

Using the data supplied by the manufacturer (http://www.magstim.co.uk), we calculate that the magnetic field strength on the cortical surface (3 mm from the coil) of our 50% stimulation is 1.5 T, giving rise to an electric field strength of 220 V/m, higher than those reported in other studies (e.g., see Moliadze and others 2003) but appropriate for our coil dimensions and geometry.

The statistical significance of the magnetic stimulation induced changes was determined by using analysis of variance (ANOVA) (with Bonferroni correction applied) and Wilcoxon test. Results were deemed to be significant when $P < 0.05$.

For this study, all TMS parameters were optimized to produce cortical suppression in the region of cortex below the coil (see Discussion).

Cortical and dLGN Recordings

In the majority of experiments, cortical activity was continuously monitored: multiunit "hash" was recorded through low-impedance electrodes (FHC, Bowdoinham, ME) implanted in the deep layers of V1. In addition, in 3 experiments, single-unit activity in the deep layers of V1 was recorded using high-impedance tungsten microelectrodes.

At the level of the dLGN, single units were recorded extracellularly using tungsten microelectrodes (FHC) vertically inserted through a craniotomy. All observations were made in the dLGN A laminae in an area less than 12° from the area centralis. The sample includes X and Y cells that were differentiated on the basis of a battery of standard tests, including the null test (linearity of spatial summation), RF size and eccentricity, type of response to flashing spots, and presence or absence of shift effect (Enroth-Cugell and Robson 1966; Cleland and others 1971; Shapley and Hochstein 1975; Derrington and Fuchs 1979). Waveforms and time stamps were stored (Plexon Inc., Dallas, TX) and off-line spike sorting (OSS) was used to assess adequate isolation of spikes. OSS allowed us to isolate individual waveforms from noise and also remove the artifact induced by TMS (Fig. 1*B*).

Experimental Design

The experimental protocol involved isolation of a single unit at the level of the dLGN and the precise mapping of its RF size and position and responsiveness to visual stimuli (flashing spots or drifting sinusoidal gratings of optimal temporal and spatial frequencies), with concurrent measurement of cortical activity. This was followed by a period or periods of application of rTMS interlaced with the same visual stimuli, followed by a period of recovery.

Responses to Visual Stimulation

As previously shown in psychophysical experiments, there is an optimum temporal interval between TMS and the presentation of a visual stimulus where TMS-suppressive effects are maximal (Pascual-Leone and others 1999; Walsh and Rushworth 1999; Juan and Walsh 2003). Therefore, in initial experiments and on the basis of the likely temporal progression of the visual signal through the thalamocorticothalamic loop, we decided to explore a range of temporal intervals by systematically varying the TMS time application around the presentation of the stimulus from −80 (TMS first) to +80 ms (TMS after) in 10-ms intervals.

Center–Surround Interactions

As demonstrated in experiments using decortication, a major characteristic of the influence of cortical feedback on dLGN cell visual responses seems to be an enhancement of the strength of the center–surround antagonism in the presence of moving stimuli, leaving the responses evoked with static stimuli (e.g., flashing spots) less affected (Murphy and Sillito 1987; Rivadulla and others 2002). Thus, here TMS was used to study the effect of cortical feedback on dLGN cell area summation properties. Visual stimuli consisted of flashed spots of varying diameter centered on the RF. Based on results derived from Responses to Visual Stimulation above, here TMS single pulses were applied 40 ms before each stimulus presentation. Here we defined the optimum response as that diameter which elicited the maximum response; the nonoptimal stimulus used for analysis was the largest stimulus used that still elicited a significant effect.

The rTMS and Visual Responses: Regulation of Response "Mode"

Trains of TMS pulses, applied repeatedly, allowed prolonged duration cortical blockade. We used this to further investigate visual responses using the longer duration stimuli such as drifting gratings. Here we applied the "6@0.1 Hz" paradigm described above. Each trial then lasted 10 s, and the grating was presented continuously. We routinely collected spikes over at least 6–8 trials. In this paradigm, we also analyzed the spike firing in terms of burst versus tonic mode. Visual responses were separated into spikes that were considered to be "tonic" and those in "bursts" and counted, as has been previously described (Guido and others 1992; Lu and others 1992; Rivadulla and others 2003). A burst consisted of at least 3 consecutive spikes with interspike intervals less than 4 ms, preceded by a silent period of at least 50 ms (for the justification of these criteria, see Rivadulla and others 2003). All spikes that did not meet these criteria were considered as tonic. In burst analysis of this data, we carefully tried to avoid false-positive bursts due to contamination from a second neuron, not only continuously monitoring the waveforms but also repeatedly examining the RF of each cell using sparse noise mapping and routinely performing autocorrelograms to verify the presence of a complete refractory period.

Results

The results presented here are derived from 34 cells recorded in the A laminae of the dLGN with RFs within 12° of the area centralis. The LGN sample comprised 18 X, 13 Y, and 3 unclassified cells. There were no obvious distinctions between the action of TMS pulses on X or Y cells or the ON and OFF center subgroups. The experimental paradigm is illustrated in Figure 1. We also recorded from 5 cortical cells directly beneath the TMS coil during simultaneous visual and TMS stimulation.

Visual Cortical Responses to Local TMS

In 3 experiments, we recorded visual-driven activity from single cortical cells during TMS stimulation. We evaluated the effect of a single TMS pulse of 50% maximal output strength, applied to the visual cortex. The histogram in Figure 2*A* shows the visual response of a layer 6 cortical cell before (left) and during TMS (right). Responsiveness recovered shortly after stimulation ceased. Figure 2*B*

shows the average visual suppression of 5 different cortical neurons to TMS. In no case did we observe a facilitatory effect of TMS on the cortical visual response.

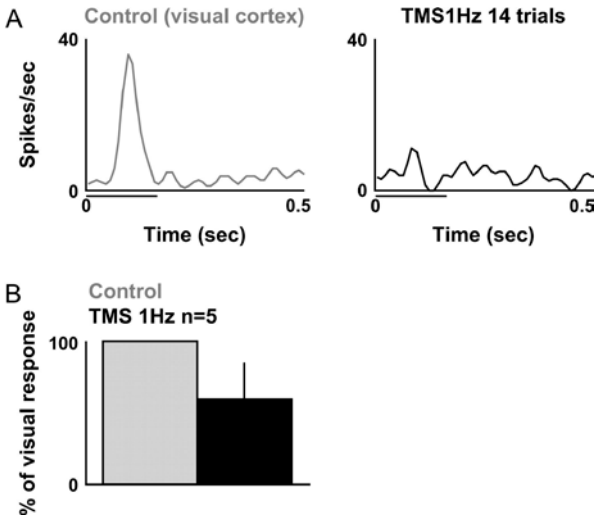

Figure 2. The effect of TMS pulses on V1 cell visual responses. (*A*) Responses of a cortical cell recorded during 1-Hz TMS. A potent visual response is seen during control visual stimulation. (*B*) The visual response is markedly reduced during TMS. (*C*) A summary histogram for the sample of 5 cells. The bar represents the standard error of the mean. The line below each of the PSTHs indicates the time for which the flashed visual stimulus was on.

LGN Cell Responses to Visual Stimulation

We used the TMS paradigm described above to examine visual responses evoked by a flashing spot on the RF center of dLGN cells. A full set of test conditions was applied to a subset of 14 cells (7 X, 5 Y, and 2 unclassified).

For punctuate disruption of corticogeniculate activity via TMS, we emphasize 3 points: the effect selectively disrupted the sustained versus the transient component of the visual response, the typical effect was a decrease in the visually evoked response, and the timing of the delivery of TMS relative to the delivery of visual stimulation was critical.

Figure 3*A* shows a typical example. The decrease in the visual response is most obvious in the later component of the visual response of this cell. This is an ON center Y cell; on the left is the control and on the right is a peristimulus time histogram (PSTH) of the visual response when TMS is delivered 40 ms preceding the visual stimulus. The reduction in the later (sustained) component of the response is very clear, 70% (from 69 to 21 spikes) versus 14% drop in the early (transient) response (60–52 spikes). Figure 3*B* shows the summary statistics for our sample of 14 LGN cells analyzed.

Figure 4 demonstrates the importance of the timing of the TMS pulse and visual stimulus onset. Significant changes in visual responses were only obtained when TMS was applied before the visual stimulus. This is easily seen in the PSTHs in Figure 4*A*. The upper PSTH shows the visual response of the dLGN cell in the absence of TMS and the 4 lower show the same dLGN cell with TMS applied at times relative to the start of the visual stimulation, indicated below each PSTH. The cell was affected only by a TMS pulse given prior to the onset of the visual stimulus, and this resulted in a decrease in the sustained component of the response. TMS following this point was ineffective. When TMS was applied 40 ms before the visual stimulus, there was no reduction in the initial component of the response (total number of spikes 101 in both cases), but in the later component, there was a decrease of 46% (number of spikes dropped from 85 to 45). A second example is shown in Figure 4*B*. The effect of TMS on responses is clearly dominated by the loss of the later component, showing 85% reduction (82–13 spikes) versus 30% (150–99) in the initial part of the response. This tendency to affect the later responses more than the initial component was evident in all cells shown to have significant separable components in their visual responses.

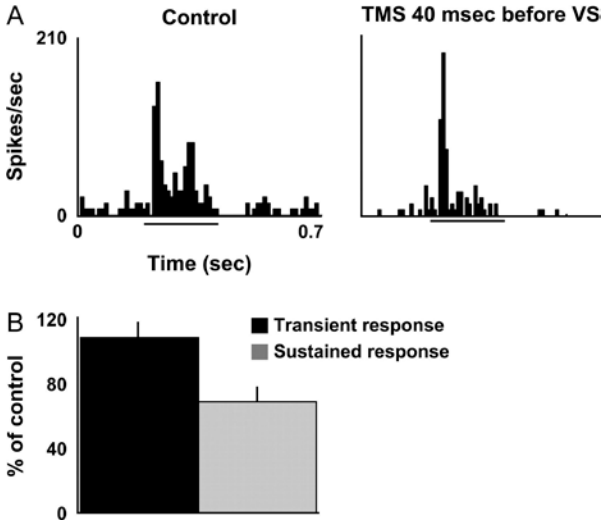

Figure 3. The effect of single TMS pulses on dLGN cell visual responses. (*A*) Responses of a single Y ON center dLGN cell before (control) and with single TMS pulses delivered each trial 40 ms before the onset of the visual stimulus. Although the effect on the dLGN was to reduce both spontaneous activity and the sustained visual response, the transient component was unchanged. The line below each of the PSTHs indicates the time for which the flashed visual stimulus was on. (*B*) Summary histogram for the sample of 14 cells.

Figure 4*C* shows the data summary for the sample of 14 cells. The optimum interval varied on a cell-to-cell basis, although there was no systematic relationship between this interval and the type of cell being tested. Disrupting visual cortical activity using single pulse TMS produced a decrease in visual responsiveness at the level of the dLGN most prominent on the later component of the responses and was time locked to the interval between the presentation of the visual stimulus and the TMS. The top histogram refers to the initial onset component of the visual response. Here TMS is essentially ineffective; we found only a small significant effect when TMS was applied 80 ms before the visual stimulus. Effects on the sustained response are shown in the lower histogram. Significant differences were achieved for all the situations when TMS was applied before the stimulus ($P < 0.05$, ANOVA), with the greatest effect obtained at 40 ms time difference ($34 \pm 6\%$, $P < 0.01$, ANOVA).

These effects appear to be the result of selective interruption of the corticogeniculate pathway. When the TMS coils were placed over somatosensory cortex that is physically closer to the dLGN, TMS pulses had no effect on dLGN visual responses (data not shown).

Center–Surround Interactions

Flashed spots of varying diameter were centered on the RF, and as demonstrated above, TMS significantly reduced the LGN cell visual responses. Stimuli restricted to the RF center were more affected by TMS than larger stimuli that also included the surround. The tuning curve illustrated in Figure 5*A* gives an example. This cell responded best to a stimulus of 2° in diameter, and responses were weaker for larger stimuli. Importantly, the reduction following TMS is most obvious for the optimal response, and the nonoptimal responses are almost unaffected. The changes in tuning follow from an effect on the sustained component of the response. TMS had minor influence on the transient visual response but seriously decreased the sustained component (Fig. 5*B*). Figure 5*C* summarizes the data for all 9 cells tested and compares the percentage of suppression for the optimal ($21 \pm 4\%$) and nonoptimal diameter stimuli ($11 \pm 5\%$). Although in both cases, responses following TMS were significantly reduced compared with control ($P < 0.05$, Wilcoxon), they were also significantly different from each other, suggesting that disrupting cortical feedback mainly affects the optimal stimulus ($P < 0.05$, Wilcoxon).

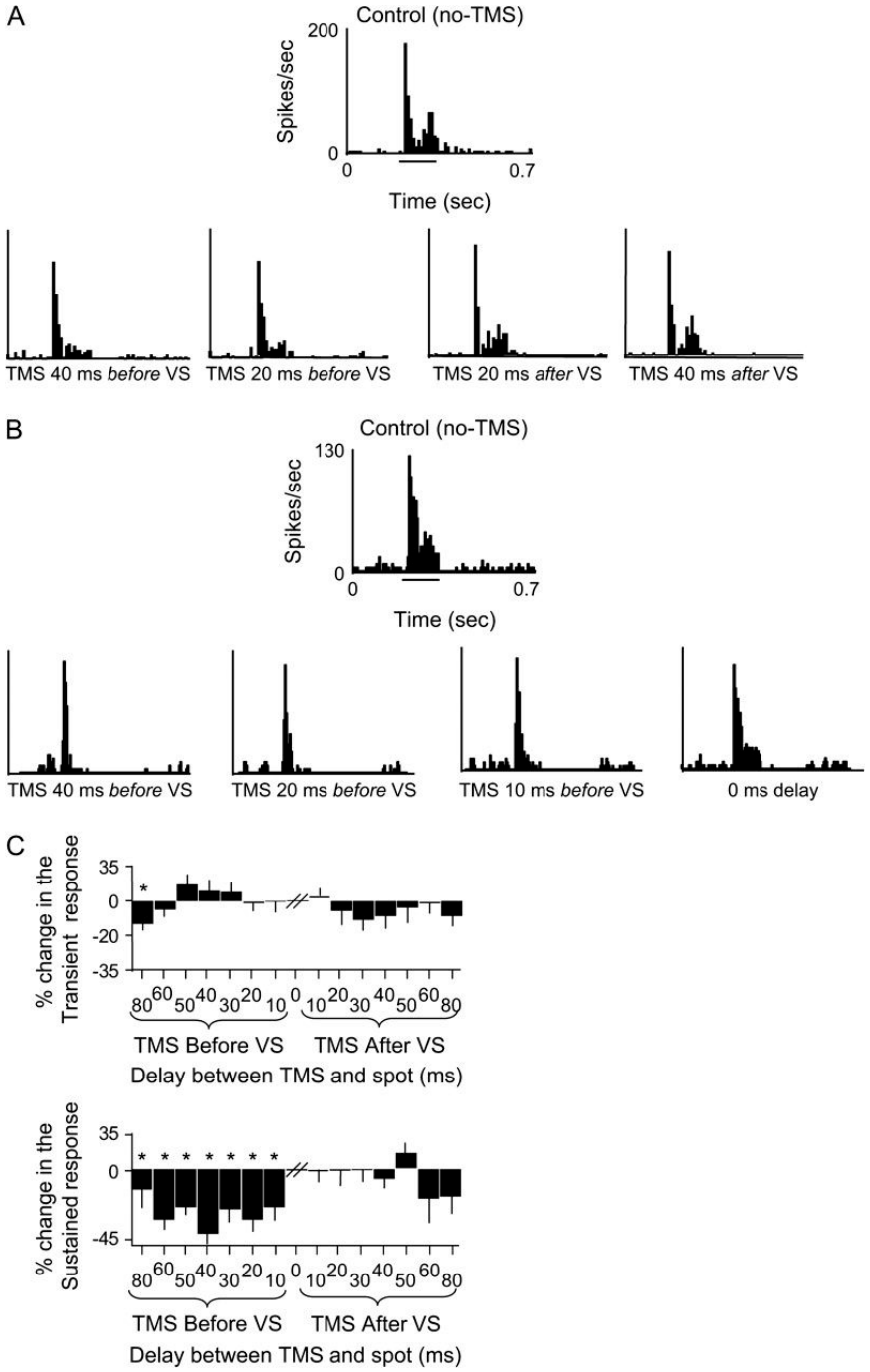

Figure 4. Critical timing and the effect of single TMS pulses on dLGN cell visual responses. (*A*) Visual responses of a single Y, ON center cell shown in control conditions in the upper PSTH. A 200-ms visual stimulus comprising a spot of light covering the RF center was repeatedly shown and the responses averaged over 20 trials, bin size 10 ms. In the lower row, this is repeated. Here a single TMS pulse was applied to the cortex during each trial at a time relative to the onset of the visual stimulus as indicated below each PSTH. The pulse was given both before (left PSTHs) and after (right PSTHs) the start of the visual stimulus. (*B*) A second example, in this case, an X, ON center cell, arranged as in Figure 2*A*. Here, however, all TMS pulses were given either just before (40, 20, and 10 ms, left 3 PSTHs) or concomitantly (right) with the onset of the visual stimulus. In both (*A*) and (*B*), the line below each of the uppermost PSTHs indicates the time for which the flashed visual stimulus was on, and this applies to all PSTHs in the figure. (*C*) Bar histograms of the change in response magnitude as a function of the relative interstimulus interval between TMS and the visual stimulus. Bars are the average change across the sample of 14 cells, and error bars indicate the standard error of the mean. *, significantly different from the control value. Upper histogram, transient (initial) component of the visual responses; lower histogram, sustained (late) component.

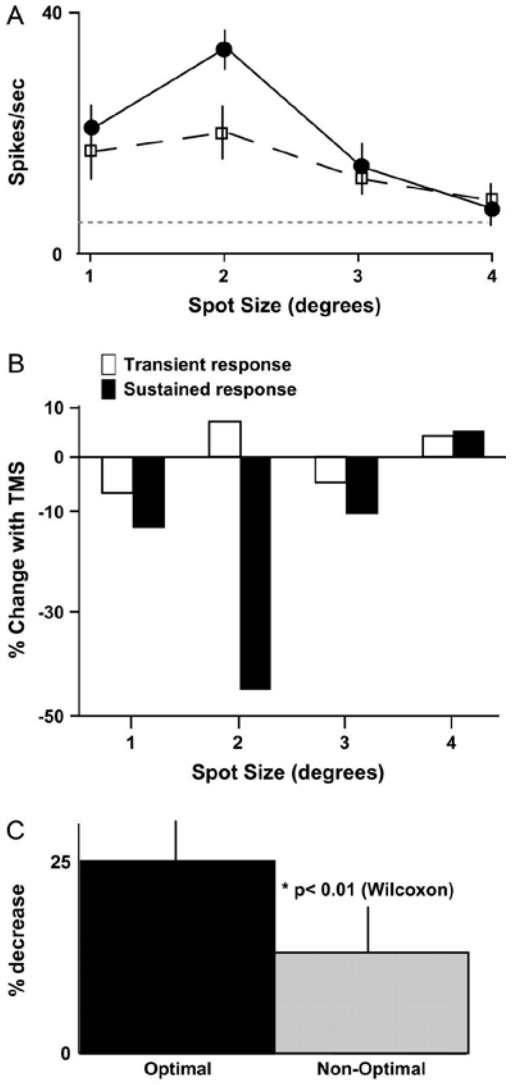

Figure 5. Center–surround antagonism and the effect of TMS. (*A*) Single-cell data for an X, ON center LGN cell. The tuning curve (solid line) shows the size of the RF as measured using spots of different sizes flashed over the center of the RF. As is typical of dLGN cells, the responses first rose to peak value as the RF center was filled and then fell as the surround was further engaged. When TMS was applied to the cortex (dashed line), response magnitude fell but was most suppressed when the stimulus was the optimum size for the RF. Visual responses obtained with nonoptimal stimuli, smaller or larger than the optimal, were less affected by TMS. The dotted horizontal line represents spontaneous activity. (*B*) Variation of the responses seen in (*A*) separated into transient and sustained components, for each size of the stimulus. Note that only the sustained response is significantly reduced. (*C*) Data from the whole sample further demonstrating this effect. The bar histogram shows the degree of response suppressing seen to each cell's optimum stimulus (black bar, left), compared with the degree of suppression elicited when the visual stimulus was nonoptimal (i.e., the largest size tested that still elicited a measurable visual response, gray bar, right). Responses are shown as the mean value for 9 cells, with the standard error of the mean.

Effect of Changing TMS Frequency on dLGN Cell Activity

Single pulses of TMS clearly had an effect on visually driven activity. They also had an effect on spontaneous activity. Figure 6A shows the cumulative result of 58 s of TMS at 1 Hz on one cell. Time 0 is the onset of each single TMS. Activity was consistently depressed for ~500 ms and then recovered. Varying the temporal parameters had a marked influence on both the degree of suppression of spontaneous activity and the time course of recovery. Whereas 1-Hz TMS suppressed activity for ~500 ms, trains of pulses (6 pulses per train delivered at 6 Hz) with an intertrain interval of 10 s (our 6@0.1 Hz paradigm, see Materials and Methods) exhibited both greater depression (maintained for at least 10 s until the next train was applied, Fig. 6B) and a longer period needed for recovery (>2 min, Fig. 6C). More quantitative analysis of the data for the whole sample (n = 14) is shown in Figure 6D. TMS at 1 Hz reduced spontaneous activity by 24 ± 8%, whereas the reduction obtained with TMS at 6@0.1 Hz was 33 ± 6%, but this was of course extended by at least an order of magnitude in the time domain following the 6@0.1 Hz stimulation.

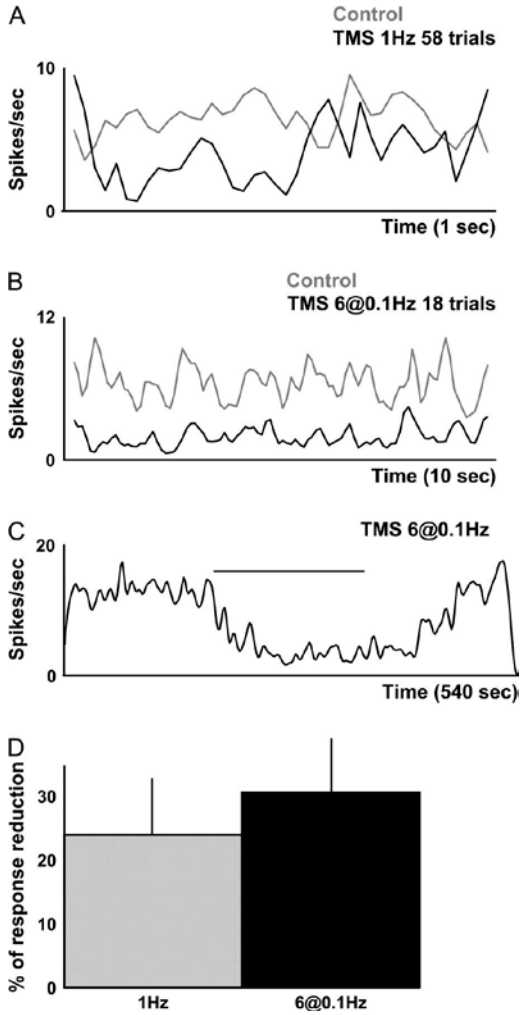

Figure 6. "Single" versus rTMS. (*A*) The effect of TMS given once each trial on the spontaneous activity of a single dLGN X, OFF center cell. The PSTH shows the control activity (gray) and that during the TMS protocol (black). Activity is reduced by the TMS, but not throughout the recording cycle. Activity is normal at the start of the trial, falls rapidly thereafter, but recovers approximately half way through each of the 1-s records. Results are the average of 58 trials. (*B*) The TMS protocol gives a 1-s burst of 6 Hz 50% intensity pulses at 0.1-Hz intertrain interval, that is, one train each 10 s (see *x* axis)—our 6@0.1 Hz stimulus protocol (see Materials and Methods). Control responses in the absence of TMS are again shown in gray and those with TMS in black. Here suppression lasted throughout the longer 10-s recording interval. (*C*) The protocol applied in (*B*) above is here shown on a cell in which the TMS pulses were applied during continuous recording over a single 540-s period. Here the effectiveness of the TMS can be seen to be continuous, without recovery such as that seen in (*A*), and to outlast the period of application by many seconds. (*D*) Quantification of the degree of suppression seen using the 1-Hz TMS and the 6@0.1 Hz TMS protocols. Note, however, that even though the TMS seemed to be only slightly more effective in strength, its temporal dynamics were greatly different.

Cortical Input Influences the Mode of Response in the dLGN

TMS delivered using the 6@ 0.1 Hz allowed longer, continuous periods of blockade. We used this to explore responses over longer periods and were especially interested in the responses to sinusoidally modulated drifting gratings, which generated the larger number of spikes necessary for analysis of firing mode.

Figure 7*A* shows the responses evoked from an ON Y cell by a drifting grating in control (gray line) and following TMS (black line). The control showed a typical modulation of the activity, phase locked to the temporal frequency of the stimulus. TMS produced a reduction in the total visual response (27%). Close observation suggested that TMS affected the duration of the response to each cycle of the grating, effectively shortening the response period (see also Fig. 8), removing the more "sustained" spikes, much as was seen for static flashed stimuli above. Full recovery (not shown) took 10 min. For all 11 cells studied with this protocol, we obtained similar results.

This response pattern to a drifting grating after TMS is reminiscent of that obtained by others when relay cells fire in burst mode (Guido and others 1992, 1995; Sherman 2001a). Interestingly, we have found a direct relationship between the decrease in the visual response and tonic firing. Figure 7*B* illustrates this relationship for the cell shown in Figure 7*A*. When the visual response was divided into

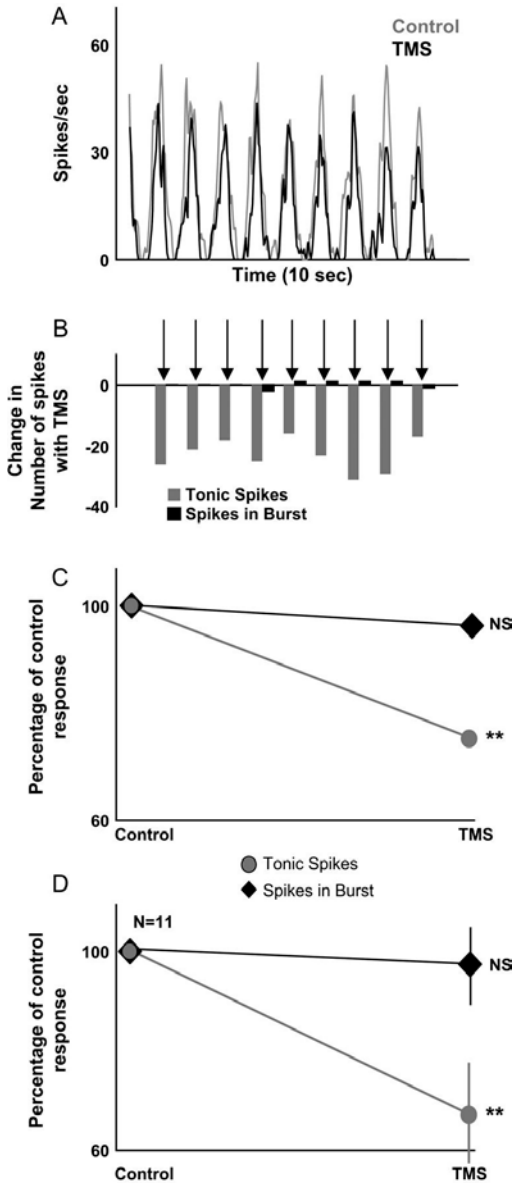

Figure 7. Effect of cortical TMS on dLGN cell burst and tonic firing. (*A*) Responses of a single dLGN Y, ON center cell to a drifting sinusoidal drifting grating. Again control responses are shown in gray. Here the responses in black are seen during application of the 6-Hz TMS protocol to the cortex. Responses are again suppressed. (*B*) Variation of the responses seen in (*A*) separated into spikes fired in bursts, and those fired in tonic mode, for each cycle of the grating. Note that only the tonic spike count is significantly reduced, and the burst count is unaffected. (*C*) Average change for the whole visual stimulus. Values have been normalized to those seen in the control situation (left) and are expressed as a percentage of this during rTMS, right. (*D*) Data for 11 cells analyzed as in (*C*) again, clearly only tonic spikes are reduced in number, burst spikes are unaffected by the TMS protocol. Values are shown ±1 standard error of mean.

spikes fired in tonic and burst modes (see Material and Methods), the number of spikes fired in bursts (and also the total number of bursts) was unaffected by the TMS protocol, whereas the number of spikes fired in tonic mode was significantly reduced, showing this reduction evenly through each cycle of grating presentation. This is most clearly seen for summed data, as shown in Figure 7*C*—tonic spike activity is significantly reduced, and the burst activity unaffected. This result was typical of the sample of 11 cells tested, as illustrated in Figure 7*D*, where again there is no significant change in the number of spikes fired in bursts during controls and the TMS-affected responses (97 ± 14% of control, $P > 0.05$, Wilcoxon), whereas tonic spikes were significantly reduced, on average to 67 ± 7% ($P < 0.05$, Wilcoxon) of the control value. It is important to note that whereas the number of spikes fired in bursts was unchanged, the percentage of the total number of spikes fired during the response (a measure often seen in the literature) was increased—this was simply a consequence of the overall reduction in spike numbers.

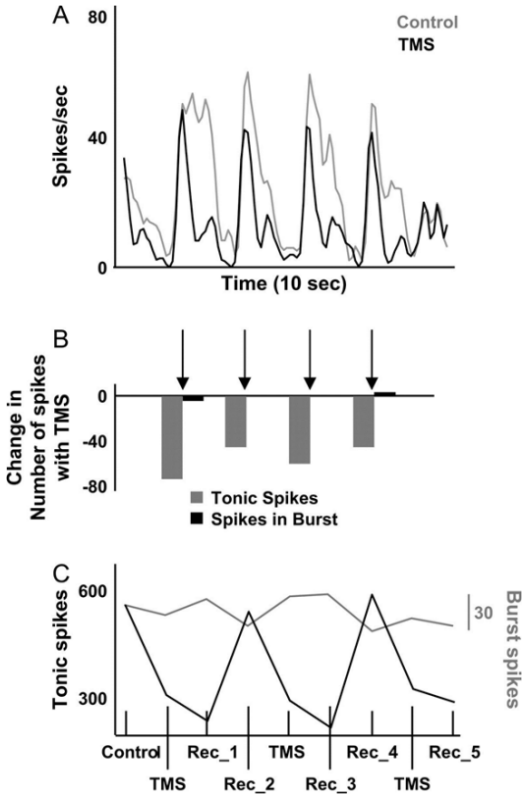

Figure 8. Reproducibility of TMS effects on tonic firing. (*A*) A second example of the protocol illustrated in Figure 7*A*, here the dLGN X, ON center cell is stimulated with a sinusoidal drifting grating. The reduction induced by application of TMS (black line) is obvious, as is the change in shape indicating the selective loss of the more "sustained" component of the grating response. (*B*) Variation of the responses seen in (*A*) separated into spikes fired in bursts, and those fired in tonic mode, for each cycle of the grating. As in Figure 7, the tonic spike count is significantly reduced, and the burst count is unaffected. (*C*) The protocol is repeated 3 times, and the analysis demonstrates again the remarkably selective effect on tonic firing, with complete recovery following the application of TMS. Recovery is not immediate but on a timescale commensurate with the dynamics suggested by Figure 6*C* above.

Figure 8*A* shows a second example of the effect of this more prolonged block of cortical activity during stimulation with a drifting grating. The effect on the more sustained component of the response is here clearly visible. Again, in Figure 8*B*, the effect is clearly derived from a reduction in tonic mode firing, and burst mode is unaffected. More importantly, as shown in Figure 8*C*, the same protocol was applied 3 consecutive times over a time course of about 40 min, with similar results each time: a fall in the total number of spikes with no significant change in the number of spikes fired in bursts. Although the reliability of this effect in this case seems remarkable, this was also seen in other cells ($n = 4$) where the protocol was applied several times.

Discussion

TMS has been extensively used to explore the nervous system, clinically and experimentally. From these studies, including the evaluation of feedback projection on perception (Pascual-Leone and Walsh 2001; Juan and Walsh 2003; for a review, see Merabet and others 2003), we know that TMS pulses can be precisely linked to a sensory stimulus and the duration of the observed effect can be controlled, varying from milliseconds to minutes, by changing the stimulation parameters, that is, number and frequency of magnetic pulses (Pascual-Leone and others 1998; Fitzgerald and others 2002). Here we use rTMS at different frequencies applied to the visual cortex to study cortical influences on thalamic responses. This represents, to our knowledge, the first attempt to use rTMS to evaluate feedback influences at the cellular level. The results of these experiments are consistent with the idea that the visual cortex provides a tonic depolarization to the LGN, increasing the RF center evoked responses in the short timescale. However, like large inactivations or ablations, our rTMS effectively silences large areas of the visual cortex—more subtle effects may follow local disturbances and may include both excitation and

inhibition (Sillito and Jones 2002; Moliadze and others 2003) or changes restricted to local regions of visual space.

Technical Considerations

Stimulation frequencies of 1 Hz are considered to be "low-frequency" stimulation and expected to induce depression of cortical activity (Chen and others 1997; Boroojerdi and others 2000; Maeda and others 2000). We directly confirmed this by simultaneously recording activity in the visual cortex. TMS pulses, delivered at 50% intensity to visual cortex, reliably reduced cortical activity for ~500 ms. This contrasts with a previously published study in a similar experimental preparation (but with some methodological differences, Moliadze and others 2003) showing that stimulation intensities higher than 50% creates a 200-ms period of depressed activity in the visual cortex, followed for a transient rebound (up to 500 ms) and a later depression. The differences in the nature and duration of the effect seen by these authors (Moliadze and others 2003) and ours could be methodological. Our induction coil was smaller (double small 25-mm coil), able to create higher intensity magnetic field (4 versus 3 T), and was seated on the skull, whereas Moliadze and others (2003) placed their coil 10 mm away from the cortex; hence, a similar output (i.e., a similar percentage of maximum strength) from our stimulator could induce a higher magnetic field in the cortex. We calculate that at a distance of ~3 mm from the skull, the 50% TMS strength will result in a magnetic field of 1.5 T and electrical field gradient of 220 V/m. In any case, our cortical data should be considered only as an indicator of TMS action and not a detailed study of cortical TMS as carried out by Moliadze an others (2003, 2005 and see below).

Significantly, our 6@0.1 Hz rTMS paradigm contains elements of both "low-" and (at least borderline) "high-frequency" stimulation. High-frequency stimulation is supposedly excitatory. Some authors have shown differential effects of this frequency when directly compared with lower frequencies (Gorsler and others 2003; Quartarone and others 2005). However, the final effect is determined by the combination of frequency with the total number of pulses, the intensity, and how they are combined. For instance, Maeda and others (2000) found a significant increase in the response at 10 Hz when 1600 pulses were applied, but not 240, and Wang and others (1996), using an experimental paradigm more similar to ours (8 Hz, 1 s, 5 s pause), found interanimal variability in the effect of rTMS, producing long term depression in some rodents' auditory cortex, but increases in others. It is clear that our 6@0.1 Hz rTMS protocol induced an effect compatible with a profound depression of cortical activity, which we could prolong as required. A possible explanation is that the decisive factor of the protocol is not the 6-Hz "intratrain" interval but the slow, 0.1-Hz "intertrain" interval. Thus, we could, in effect, be using the more powerful low-frequency TMS, resulting in a deeper and longer effect on visual cortex. Our control stimulation of somatosensory cortex not only confirms the lack of a direct effect on thalamus (because the relative distance and angles of the structures from the coil involved were maintained) but also shows that the lateral spread of the effect was less than the distance between these stimulation sites on the cortical surface. We did not systematically map the spatial extent of the cortical suppression zone; however, it is likely, given the size of the cat brain and the spatial resolution of TMS (for a detailed description, see Pascual-Leone and others 2002) that our stimulation effectively covered the primary visual cortex and that the effect was uniform across this region.

Hence, we assume that our TMS is affecting most of primary visual cortex (but probably including area 18), and is inducing a temporary block of the majority of cortical feedback, without direct effect on the dLGN. More complex explanations exist, involving both cortical excitation and inhibition. One such scenario involves the enhancement of inhibition locally and selectively within the LGN itself, resulting from enhanced cortical drive to these cells (itself the result of complex effects of TMS upon cortex, see Moliazde and others 2003). However, our sample of cortical cells suggests that the major effect of TMS in our hands is suppression of cortical activity, with resultant loss of excitatory drive to the LGN, and this is therefore the simplest hypothesis to account for our findings.

The fact that TMS of the cerebral cortex significantly changes thalamic properties through feedback mechanisms has important consequences on the interpretation of many TMS results. Even if the direct action of TMS is local, its actual effect could be much more far reaching, affecting other systems whether primary sensory or those interacting with higher thalamic regions such as the pulvinar.

Cortical Influences on the Thalamus

In a novel application, we believe that rTMS as applied here strongly and reversibly suppressed cortical feedback to the dLGN, providing a powerful tool in probing this large pathway. These effects were robust and selective in perturbing the visual response of dLGN cells. Thalamic visual responses evoked by static stimuli were decreased mainly in the sustained component. Although contrary examples exist, methodological differences are sufficient to explain our findings (e.g., Murphy and Sillito 1987

[lesion of cortex: intra-animal comparison of center–surround antagonism in control versus lesioned hemispheres]). Our data with rTMS are in keeping with several previous findings, demonstrated by other means (see e.g., Rivadulla and others 2002 [pharmacological blockade of corticofugal input]; Wörgötter and others 1998 and reviewed in Wörgötter and others 2002 [comparison of LGN responses during different EEG states]).

Our control recordings in the visual cortex indicate that this effect is due to suppression of cortical activity for brief periods after TMS, hence a drop in activity of the direct cortical excitatory inputs onto relay cells (Wörgötter and others 1998), probably operating through metabotropic glutamate receptors (Godwin, Van Horn, and others 1996; Rivadulla and others 2002), which normally maintain a tonic depolarization in the thalamus. The observed effect is more apparent when the cell is stimulated with its preferred stimulus (i.e., a stimulus that maximizes the excitatory input but concurrently minimizes inhibitory drive). When stimulated with a less effective visual stimulus, the amount of suppression due to the TMS is less. This suggests a degree of selectivity in the corticofugal feedback to the dLGN, in keeping with previous reports in the visual system (Tsumoto and others 1978; Murphy and Sillito 1987; Wörgötter and others 1998; Rivadulla and others 2002) and also in somatosensory (Canedo and Aguilar 2000; Ghazanfar and others 2001) and auditory systems (Zhang and others 1997; Suga and others 2002).

Response Mode

Thalamic cells can fire action potentials in tonic or burst mode (Jahnsen and Llinas 1984). TMS inactivation of cortex appeared to have a peculiar effect on response mode to visual stimulation: the number of tonic spikes dropped significantly but appeared to have no influence on the number of spikes fired in burst mode. This contrasts with the implications of previous work (Funke and Wörgötter 1995; Wörgötter and others 1998), which suggested that burst firing should increase when cortical influences were minimized—because the cells would remain in burst firing mode for a longer period without "converting" to tonic mode. The differences in the 2 results may be methodological. It is clear from our data that the effect of TMS is to reduce the visual response magnitude of dLGN cells and that this effect is seen in changes to tonic firing. A small reduction in relay cell membrane potential could disproportionately decrease tonic firing without affecting burst firing levels significantly. Burst firing is found primarily at the start of visual responses but may be critical for normal visual function, constituting localized visual "surprise" (see Rivadulla and others 2003; Marin and others 2005). Levels of bursting may be controlled by other, noncortical influences, such as modulatory influences from the parabrachium, basal forebrain, and locus coeruleus (all of which may contribute to the results obtained by Funke and Wörgötter 1995; Wörgötter and others 1998) and even the rate of retinal spontaneous and visually elicited activity. Thus, control of burst firing seems much more complex, as recent evidence suggests (Wolfart and others 2005; Bezdudnaya and others 2006), perhaps even utilizing local γ-aminobutyric acid–mediated tonic inhibition (Cope and others 2005).

Our novel use of TMS over the visual cortex here reveals that in normal function there is cortically driven enhancement of thalamic tonic firing. However, levels of burst firing remain unchanged by alterations of cortical input, and it remains open to consideration what the actual role of such bursting is during normal visual function.

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