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The influence of the corticothalamic projection on responses in thalamus and cortex

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We review results on the *in vivo* properties of neurons in the dorsal lateral geniculate nucleus (dLGN) that receives its afferent input from the retina and projects to the visual cortex. In addition, the dLGN receives input from the brain stem and from a rather strong corticothalamic back-projection, which originates in layer 6 of the visual cortex. We compare the behaviour of dLGN cells during spontaneous changes of the frequency contents of the electroencephalograph (EEG) (which are mainly related to a changing brain stem influence), with those that are obtained when experimentally silencing the corticothalamic feedback. The spatial and temporal response properties of dLGN cells are compared during these two conditions, and we report that the neurons behave similarly during a synchronized EEG state and during inactive corticothalamic feedback. In both situations, dLGN cells are rather phasic and their remaining tonic activity is temporally dispersed, indicating a hyperpolarizing effect. By means of a novel method, we were able to chronically eliminate a large proportion of the corticothalamic projection neurons from the otherwise intact cortex. In this condition, we found that cortical cells also lose their EEG specific response differences but, in this instance, probably due to a facilitatory (depolarizing) plasticity reaction of the remaining network.

Keywords: visual thalamus; state dependence; corticothalamic feedback; targeted cell death; gating processes

1. INTRODUCTION

The visual system consists of multiple nested feedback loops, which link neurons with each other at all hierarchical levels above the retina. The first loop from the dLGN to the (primary) visual cortex and back consists of a massive bundle of fibres and provides *ca*. 50% of the synapses in the dLGN. Despite its substantial size only relatively weak and non-uniform effects on the responses in dLGN cells have been reported for this projection. This may be due to the fact that almost all experiments which address the action of the corticothalamic projection were performed either *in vitro* or in anaesthetized *in vivo* preparations. In addition, at the present time, recording cortical cells during an inactive feedback loop, which might also provide more insight into the closed loop properties of this feedback system, is not possible. The earliest experiments in which the corticothalamic projection was inactivated suggested a rather broad, unspecific facilitatory action from the cortex onto the dLGN (Kalil & Chase 1970; see also Singer 1977); later it was found that the corticothalamic feedback can influence the spatial structure of dLGN RFs (Vidyasagar & Urbas 1982; McClurkin & Marrocco 1984; Murphy & Sillito 1987; Sillito & Murphy 1988; Sillito *et al.* 1993, 1995; Cudeiro & Sillito 1996). It is probable that corticothalamic feedback is organized in an antagonistic 'centre/surround' fashion—exerting a facilitatory influence within a centre of topographic match (*ca*. 1–2°) but a suppressive effect from surrounding regions (Tsumoto *et al.* 1978). This may contribute to dLGN receptive-field tuning but may also affect the saliency of stimuli via focal changes in the contrast/response gain influencing visual attention (for a review on low-level pre-attentive effects see Suder & Wörgötter (2000)). Changes in the temporal structure of visual activity (Funke & Wörgötter 1997) are suited to the support of these processes, for example, corticothalamic control of temporal synchronization of dLGN spike activity (Sillito *et al.* 1994).

These approaches addressed the influence of the corticothalamic projection onto the visual physiology of dLGN cells. Another set of experiments was performed to investigate its role in the generation of specific brain states, as reflected by the structure of the EEG. Corticothalamic projections close a loop that is involved in the generation and synchronization of fast (20–50 Hz) and slow (less than 15 Hz) oscillations in thalamocortical networks, characterizing activated (less synchronized) and sleep-like (synchronized) states, respectively (see Steriade 1997). The corticothalamic projection has both: locally restricted and highly divergent components (Murphy & Sillito 1996; Murphy *et al.* 2000), the latter being especially suited to support long-range thalamocortical synchronization of

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thalamically generated rhythms such as sleep spindles and δ-waves (Contreras & Steriade 1996; Contreras *et al.* 1997).

In addition to their action at ionotropic glutamate receptors (Scharfman *et al.* 1990), corticothalamic inputs were found to trigger slower intracellular processes via metabotropic glutamate receptors (McCormick & Von Krosigk 1992; Rivadulla *et al.* 2002). This offers a mechanism which allows for long-term changes of thalamic responsiveness such as that demonstrated for the so-called 'response augmentation' in cat (and monkey) lateral geniculate relay cells (Cudeiro *et al.* 2000).

The corticothalamic feedback also seems to be involved in the state-dependent control of the general responsiveness of thalamic relay cells. A similar reduction of visual responses of dLGN relay cells is seen during EEG synchronization (δ-waves) and during inactivation of corticothalamic feedback (Funke & Eysel 1992). In particular, it was observed that the activity of layer 6 of the primary visual cortex changes during changes in the EEG pattern (Singer *et al.* 1976; Livingstone & Hubel 1981). This, however, also suggested that, in an experiment, effects induced by a change in the EEG can easily be confounded with those induced by cortical inactivation. For example, an increase in δ-activity in the EEG will lead to a similar, if not stronger, reduction of dLGN activity to that induced by silencing the cortex (Funke & Eysel 1992; Wörgötter *et al.* 1998*a*).

We will, therefore, mainly review results which juxtapose EEG-related effects with those induced by inactivating the corticothalamic projection. Furthermore, we will summarize the results regarding the influence of the corticothalamic loop onto *cortical* responses during different EEG states. In part, these results could be obtained by a novel method, which allowed for a specific, apoptotic elimination of a substantial proportion of the corticothalamic projection neurons from within the otherwise intact cortex.

2. THE INFLUENCE OF THE EEG STATE ON THALAMIC CELL RESPONSES

It is known that the level of excitation at a dLGN cell is reduced during an EEG state that is dominated by δ-waves (Livingstone & Hubel 1981; Sawai *et al.* 1988; Funke & Eysel 1992; Li *et al.* 1999). This state is in a non-anaesthetized situation usually associated with deep sleep. Even in an anaesthetized preparation, strong spontaneous transitions between a δ-wave-dominated EEG (so-called *synchronized* EEG) and an EEG of reduced δ-wave activity (so-called *less-synchronized* EEG) can be observed. Therefore, we expected that during synchronized EEG the net excitation at the dLGN cells would be reduced. Figure 1*a* shows this effect for 200 s of ongoing recording of a dLGN cell during stimulation with a flashing dot (100 sweeps each lasting 2 s). The superimposed EEG traces show that δ-waves are more pronounced between stimulus sweeps 25 and 75, when tonic-dLGN light responses disappeared (figure 1*b*). During the other sweeps, a less-synchronized EEG was observed and the cell demonstrated a more pronounced tonic-firing pattern. In figure 1*c* we plot the mean dLGN firing rate (thin line) against the relative spectral power of the δ-range in the EEG (1–4 Hz) for a different cell. Both traces were averaged and strongly low-pass filtered in order to cancel all high-frequency oscillations and emphasize the gradual increase in EEG δ-activity, which is accompanied by a correlated decrease in mean dLGN firing rate. A correlation of this type was found whenever the EEG showed slow changes in δ-activity (Li *et al.* 1999).

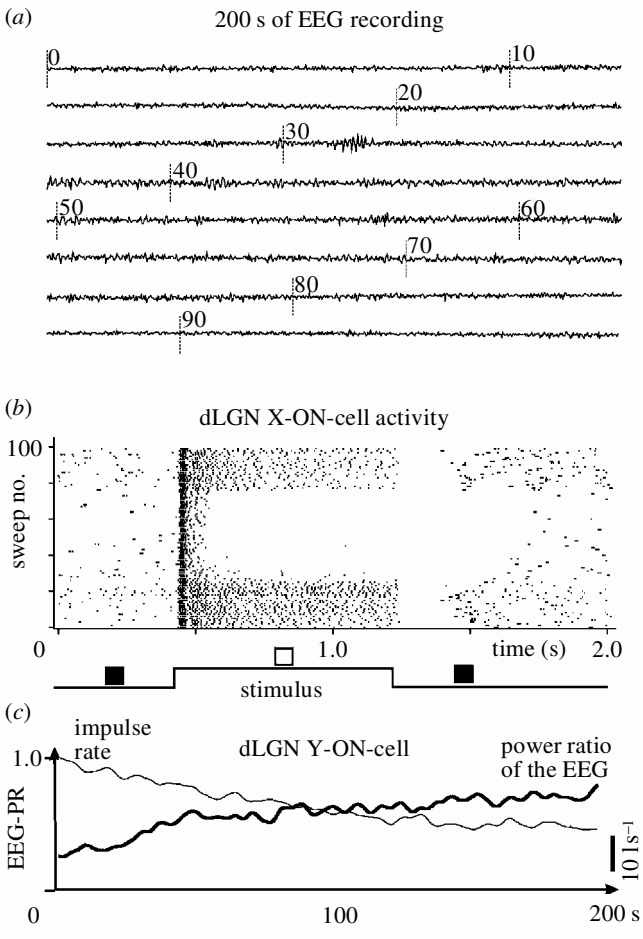

Figure 1. Influence of the EEG state on the neuronal responses in the dLGN. (*a*) EEG trace recorded for 200 s, showing pronounced δ-waves in the middle of the trace. Numbers indicate the corresponding stimulus repetition ('sweep'). (*b*) Dot raster diagram of an X-ON-cell response recorded simultaneously with the EEG trace in (*a*). The stimulus (flashing bright spot, 1.0°, contrast 0.9) timing diagram is depicted at the bottom of the diagram. The cell response is very phasic as soon as strong δ-wave activity is found in the EEG (middle part of the recording). During less-synchronized EEG, pronounced tonic responses are observed. (*c*) Normalized mean impulse rate and EEG power ratio of a different cell (Y-ON-cell) also stimulated with a flashing bright dot. The impulse rate drops as soon as the low-frequency components in the EEG increase. (Modified from Wörgötter *et al.* 1999.)

In an earlier report we demonstrated that dLGN cells have preferred 'interval modes' for firing, such that multipeak INTHs are obtained for most cells when analysing their spike trains in a specific way (Funke & Wörgötter 1995). Thus, the transition between synchronized and less-synchronized EEG not only affects the tonic firing of the cells but is also reflected in a changed interval mode

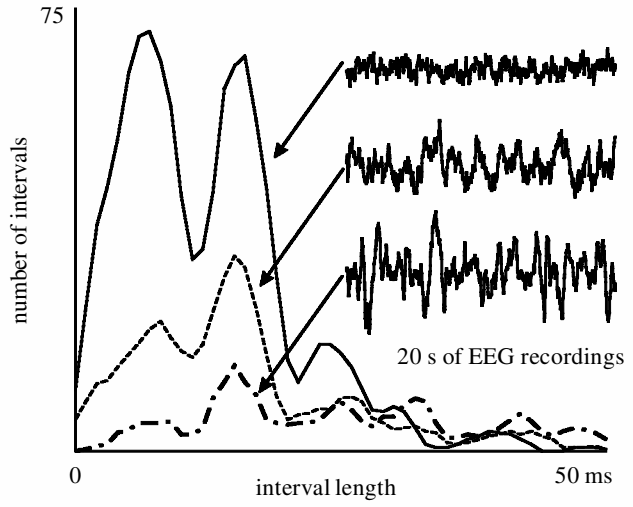

Figure 2. INTHs from an X-ON-cell stimulated with a flashing bright spot (2.0°, contrast 0.9, 100 sweeps, 2 s each) recorded during different EEG states. Short traces of the corresponding EEG recording are shown in the insets. Multiple peaks are clearly visible in each INTH. Peaks centred on longer intervals (so-called higher-order peaks) start to dominate during more synchronized EEG states. (Modified from Wörgötter *et al.* 1998*a*.)

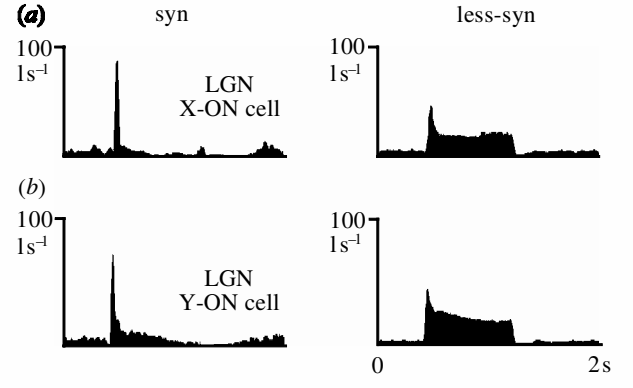

Figure 3. PSTHs from an X-ON-cell (*a*) and a Y-ON-cell (*b*) recorded during different EEG states. Both cells respond rather phasically during synchronized EEG and more tonically during less-synchronized EEG. Stimuli were: (*a*) spot 0.3°, contrast 0.9; (*b*) spot 1.0°, contrast 0.9. (Modified from Wörgötter *et al.* 1998*b*.)

pattern. This is exemplified in figure 2. The EEG traces reflect a continuous transition from a less-synchronized to a strongly synchronized EEG. (The regular INTHs shown have been obtained by averaging several pixel lines from a cross-section of the corresponding intervalograms of the activity of an LGN X-ON-cell; Funke & Wörgötter 1995.) As expected, activity decreases and, in addition, it is clearly evident that the fundamental (leftmost) interval mode decreases during increasingly synchronized EEG at the cost of relatively larger higher-order interval modes.

Figure 2 does not adequately demonstrate the tremendous impact that an EEG change can exert on the thalamic cell behaviour. Therefore, in figure 3, we show a few PSTHs of dLGN cells recorded during synchronized and less-synchronized EEG. The same cell changes its firing characteristic completely when such an EEG transition occurs. During a less-synchronized EEG, the initial phasic

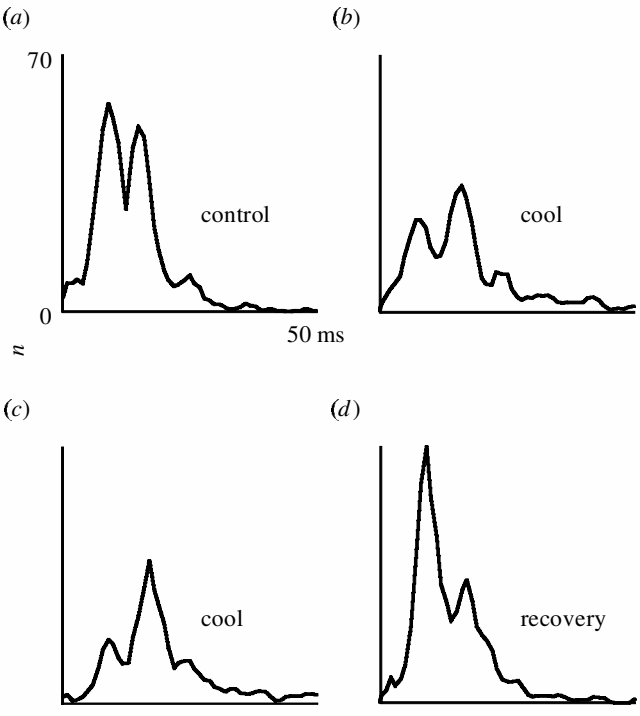

Figure 4. INTHs from a Y-ON-cell stimulated with a flashing bright spot (1.0°, contrast 0.9, 100 sweeps, 2 s each) recorded during cortical cooling. The INTHs were obtained from a temporally localized cross-section through the corresponding intervalogram of these cell responses (see fig. 2 in Wörgötter *et al.* 1998*a*). Multiple peaks are clearly visible in each INTH. Higher-order peaks dominate during cooling. Total number of spikes in each recording: (*a*) 7024; (*b*) 6769; (*c*) 4875; (*d*) 6577.

response is followed by a pronounced tonic response component, which is almost absent during synchronized EEG.

3. REVERSIBLE INACTIVATION OF THE CORTICOTHALAMIC FEEDBACK

Figure 4 shows typical INTHs obtained with cortical cooling during stimulation with a flashing light-spot stimulus. In this cell, prolonged inactivation leads to a dominance of the second peak in the interval histogram accompanied by a reduced mean firing rate of the tonic response, as can be judged from the total number of spikes in each recording (see legend to figure 4). During recovery, the cell almost reacquires its original response characteristic.

In all cases, the final result of cortical inactivation was a reduction of the firing rate in the recorded dLGN cell. However, in general, we observed a rather high degree of variability concerning the inactivation effect. Fluctuations in the (decreased) impulse rate of 10–15% between two subsequent recordings were quite common.

4. HOW TO CONTROL FOR EEG EFFECTS

The results obtained above clearly demonstrate that experimentally induced effects of cortical inactivation can easily been confounded with EEG-related effects. Therefore, at least a reliable analysis of the frequency content

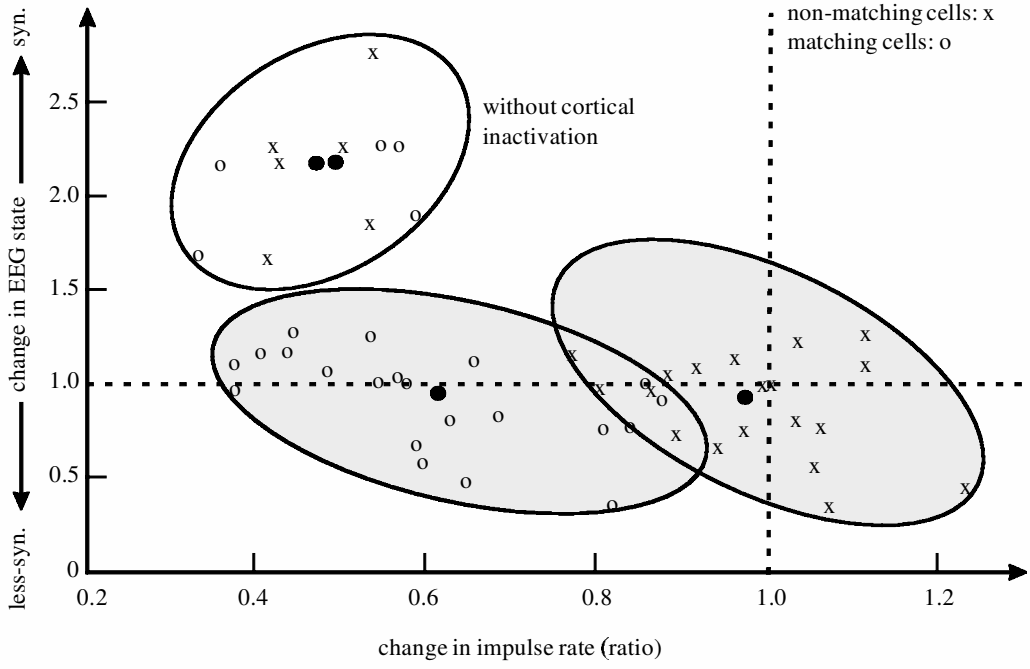

Figure 5. EEG changes compared with changes in mean impulse rate for dLGN cells recorded at a site that topographically matched the cortical inactivation site ('matching cells') as compared with a control group recorded simultaneously from a non-matching site. The EEG remained unchanged at a ratio of approximately one in both groups. Accordingly, no change in impulse rate was found in the control group (non-matching cells). The other group, however, was affected by cortical cooling and the impulse rate dropped. The recording group at the top of the diagram shows cells without cortical cooling but during a strong increase in the low-frequency components in the EEG. Both parameters covary in these cases. (Modified from Wörgötter *et al.* 1998*a*.)

in the EEG is required in order to separate the EEG stages. In addition, in many cases we performed double-unit recordings in the dLGN, where one recording site matched the cortical inactivation site, whereas the other site did not. This allowed us to distinguish the effects of cortical inactivation from those related to EEG changes by comparing the results from both recording sites. While this is experimentally more demanding, we suggest that this is good praxis to provide a reliable explanation of effects.

Figure 5 plots changes in mean impulse rate (*x*-axis) against EEG changes (*y*-axis) for cells that match the inactivation side as compared with 'non-matching' cells. The results for non-matching cells centre on a mean of approximately one. Thus, rate and EEG changes in this control group are random and relatively small. The matching cells, on the other hand, centre on 0.609/0.952. Thus, the firing rate is reduced by almost a factor of two as compared with the control group, while the EEG remained the same. The third, smaller, cluster at the top of the graph illustrates how a few matching/non-matching cell pairs react when comparing two obviously different EEG states. These particular cell pairs in the top cluster are taken from the same cell group, which constitutes the other two clusters below but without cortical inactivation. EEG effects are very strong and the mean δ-power change is 2.2. In comparison with the situation observed during cortical inactivation, we now find a clear covariation of both parameters. In summary, figure 5 demonstrates that EEG effects can be clearly separated from the experimentally induced effects by this control method.

5. REDUCED EXCITATION OR REDUCED DISINHIBITION?

The gross effect observed during cortical inactivation in this and other studies (Kalil & Chase 1970; Baker & Malpeli 1977) is the reduction of the firing rate in the dLGN cells. An increased firing rate while the cortex is active could, in principle, result from a direct facilitatory cortical influence (figure 6, S1, black connection). However, it is well known that part of the corticothalamic fibres terminate on inhibitory interneurons in the dLGN (Weber *et al.* 1989). Thus, activation of the outer neuron in a chain of two connected inhibitory interneurons (figure 6, S2, black connections) would ultimately lead to disinhibition of the relay cell, resulting in an increased firing rate. Inhibitory actions (i.e. via one interneuron) have also been reported for distinct stimulus situations (Sillito *et al.* 1993; Cudeiro & Sillito 1996), but facilitatory actions seem to dominate. These two alternatives could be tested by a combination of cortical inactivation and simultaneous pharmacological manipulation in eight dLGN relay cells, which all demonstrated a similar behaviour. Figure 6 shows a sequence of recordings from a dLGN Y-ON-cell obtained under different conditions. The stimulus was a light-spot of size 2.5°. Following the control recording, a small amount of GABA was applied (figure 6*b*) at the cell, which efficiently simulates an increase of inhibition, so that the interval pattern shifts strongly to higher-order peaks (Wörgötter *et al.* 1998*a*). GABA application was then continued at the same level but, in addition, we applied BICU with increasing dosage (10–20 nA; figure

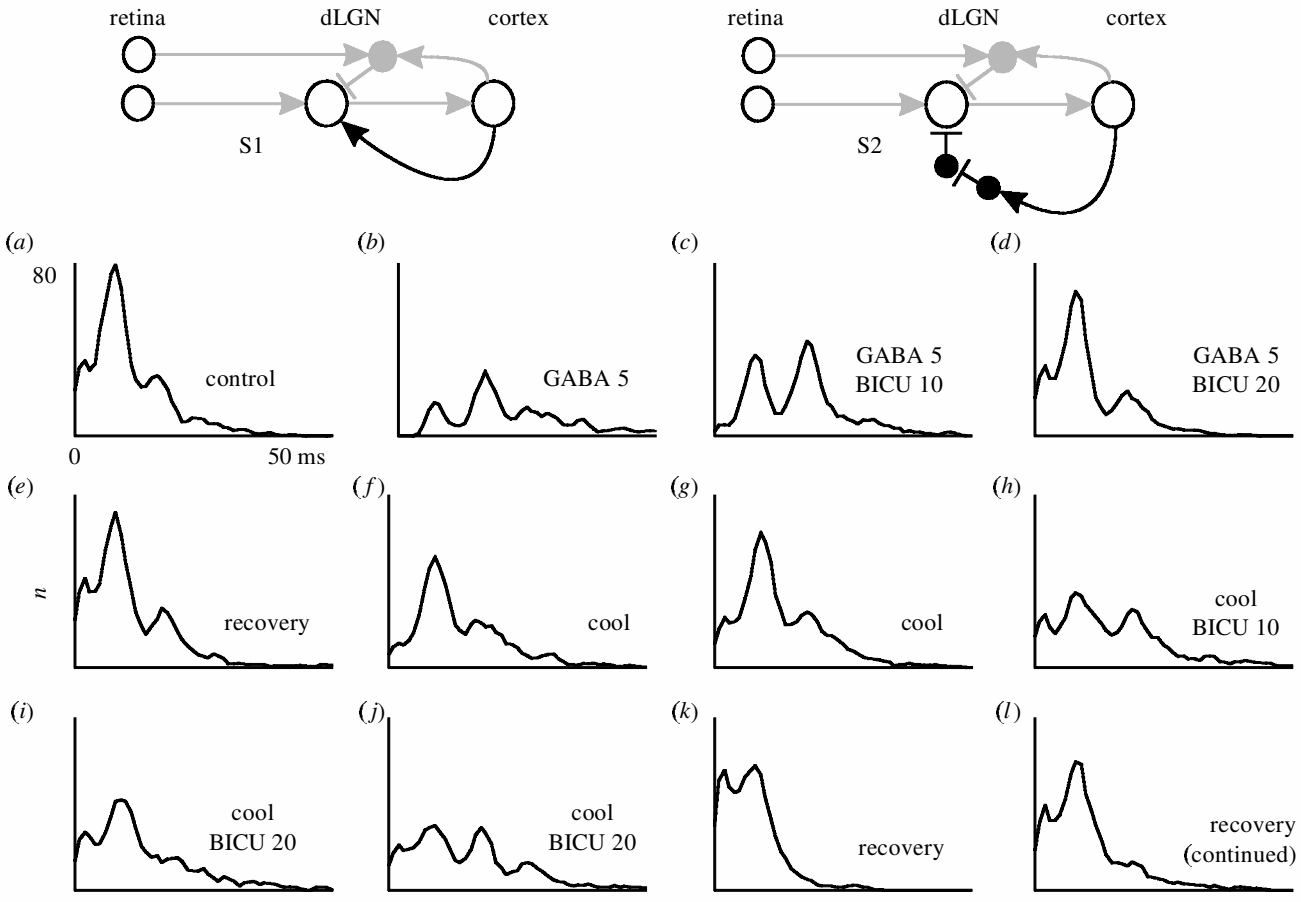

Figure 6. Interaction of cortex inactivation with disinhibition of dLGN relay cells by BICU. Simplified connection scheme of the primary visual pathway showing the pathways for corticothalamic facilitation (S1) or disinhibition (S2) in black. Combination of cooling the cortex and micro-iontophoresis of GABA and BICU in the dLGN (Y-ON-cell, flashing spot stimulus, size 2.5°, contrast 0.9). For further explanation see text. (Reproduced with permission from Wörgötter *et al.* 1998*a*.)

6*c*,*d*). As expected, the inhibitory GABA effect could be almost totally antagonized and the ejection current of BICU (20 nA) was adjusted such that an optimal antagonizing effect was obtained. Recovery (figure 6*e*) demonstrates that these effects are reversible. In the next step, drug application was stopped and cortical cooling started. Two recordings are shown (figure 6*f*,*g*) which demonstrate the reduction of dLGN activity during cooling, and also show that significant fluctuations in the total number, n, of spikes are observed even in subsequent records (figure 6*f*: $n = 6281$; figure 6*g*: $n = 6795$). As discussed above, the cooling effect is not as reliable as the direct drug-induced effects shown in figure 6*b–d*.

If the cooling effect was due to the inactivation of a disinhibitory circuit (e.g. figure 6, S2), then increased inhibition at the relay cell should be the basis of the reduced activity. Consequently, in this case we would expect to be able to strongly antagonize the cooling effect with BICU. Contrary to this assumption, BICU did not antagonize the cooling effect (figure 6*h–j*). This suggests that the facilitatory effect of the corticothalamic feedback is predominantly mediated by direct excitatory connections (e.g. figure 6, S1) and not by disinhibition.

6. THE INFLUENCE OF THE CORTICOTHALAMIC FEEDBACK ON THE TEMPORAL DISPERSION OF dLGN FIRING

During cortical inactivation, the activity in the dLGN was reduced and higher-order interval peaks dominated

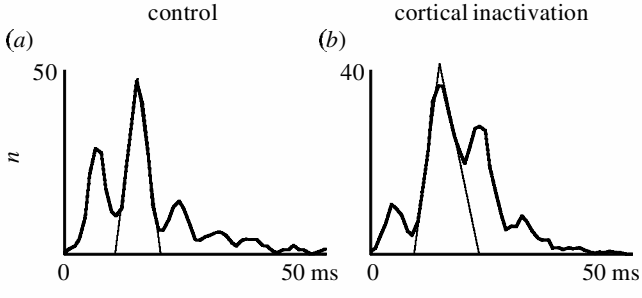

Figure 7. Cortical inactivation leads to a broadening of the interval peaks in dLGN INTHs (X-ON-cell, stimulus: spot 1.5°, contrast 0.9). (*a*) Control with sharp second INTH peak (see fitted straight lines). (*b*) All peaks broaden during cortical inactivation by bulk GABA micro-iontophoresis (compare fitted straight lines at the second peak).

(figure 4). As an additional rather pronounced effect, however, we observed a widening of the interval peaks. Figure 7 shows one example of an interval histogram obtained from a dLGN cell before and during cortical cooling. Triangles were fitted by eye to the first interval peak allowing for a comparison of the INTH width under both conditions—control and cortical inactivation. A significant broadening can be observed. Statistical analysis showed that this effect leads to a width of the peak that is, on average, 25% wider during cortical inactivation than before. As opposed to cortical inactivation, cortical stimulation, which was performed in several experiments by

micro-iontophoretical application of glutamate, leads to a sharpening of the INTH peaks. In summary, we found that in 69 cells cortical inactivation leads to a widening of the interval peaks in 57% of the cases while only 18% showed a sharpening (15% no change). Cortical stimulation, however, made the peaks sharper in 46% of the cases (30% widening, 23% no change).

7. THE INFLUENCE OF THE CORTICOTHALAMIC PROJECTION ONTO CORTICAL CELL RESPONSES

We will describe the results obtained with a novel method of targeted apoptotic cell-death induction (Macklis 1993; Sheen & Macklis 1995; Magavi *et al.* 2000; Scharff *et al.* 2000; Shin *et al.* 2000) in layer 6 of the cortex. A summary of this method is given in Appendix A; its goal is to allow for specifically eliminating a large proportion of the corticothalamic projection neurons without damaging other cells. Thus, we arrived at a situation where the corticothalamic feedback was chronically removed from within an otherwise intact cortical network. This gave us a unique opportunity to record from the cortical cells (as well as LGN cells) in a situation where the feedback is substantially reduced, if not almost eliminated.

In the first step, we analysed the effect of the method. We found that, on average, 61% of targeted cell population had vanished after *ca*. 14 days following treatment. A histological comparison between treated animals, sham control and untreated controls confirmed that this technique is absolutely non-invasive, leaving the remaining cortical network intact.

In the next step, we obtained recordings from the remaining cortical neurons and compared their responses with those recorded simultaneously from cells in the untreated hemisphere.

In order to assess to what degree elimination of corticothalamic neurons in layer 6 affected the physiological properties of the remaining cortical neurons, we recorded the responses of 76 individual cortical neurons. It is known from prior studies that the temporal response properties of cortical neurons, in particular, are significantly different during different EEG states (Ikeda & Wright 1974; Singer *et al.* 1976; Livingstone & Hubel 1981). These differences are mainly induced by state-dependent changes in brainstem activity, but it has been proposed that they are also influenced by changes in corticothalamic activity (Funke & Eysel 1992; Wörgötter *et al.* 1998*a*).

Thus, a certain predictable dependence of cortical response properties on EEG states exists which can be used to assess the effects of targeted cell death by means of a direct comparison of the responses from simultaneous recordings in the control and experimental cortex during different EEG states. We found that elimination of corticothalamic neurons had striking effects on cortical response properties, abolishing the normal dependence on the EEG state. In control cortex with intact corticothalamic feedback circuitry, longer and more pronounced tonic responses occur during less-synchronized EEG states, as compared with shorter, more phasic responses during synchronized EEG (δ-wave-dominated EEG). Figure 8 *a*,*b* shows two examples of this quite typical behaviour. The diagrams show spatio-temporal RF plots of the activity of the control neurons recorded at the central cross-section through their RFs. In comparison, figure 8*c*,*d* shows two simultaneously recorded neurons from the experimentally treated hemisphere. In contrast to the responses of neurons in the control cortex, tonic responses in the experimental cortex during synchronized EEG were significantly increased; in some cases, they even exceeded responses observed during less-synchronized EEG, in duration and/or amplitude. Statistical analysis showed that tonic responses became, on average, $77 \pm 14\%$ stronger and $64 \pm 10\%$ longer compared with control during episodes of synchronized EEG. In this way, in experimental cortex, responses obtained during both EEG states become indistinguishable. The analysis also clearly showed that measurable response alterations *only* occurred during synchronized EEG, while no changes were observed during less-synchronized EEG. In addition, we found that non-specific neuronal electrophysiological characteristics, including spontaneous activity, remained unchanged.

A second, subtler effect was also revealed through statistical analysis. We found a covariation of tonic RF width and tonic response amplitude (i.e. tonic RF width increases with increasing tonic response amplitude) in experimental hemispheres. This is in contrast to the normal finding that the width of the tonic RF remains constant in both EEG states, irrespective of the higher amplitude during less-synchronized episodes (Eyding *et al.* 2002).

The corticothalamic projection cells also provide a strong intracortical collateral input to layer 4. Thus, it cannot be ruled out that the cortical effects observed do not originate from the disturbed cortocothalamic loop; instead, they could be the result of the equally disturbed collateral network. However, similar observations were made when recording from 36 dLGN cells after targeted cortical cell death (data not shown). In the LGN we also found that the normally observed EEG-related differences between responses measured during synchronized, as compared with less-synchronized, EEG vanish in the experimental animals. Similar to the cortical results in the LGN, this is due to an increase in responsiveness during synchronized EEG. The similarity of LGN and cortical results argues against a strong effect from the disturbed collateral projection system.

These results are not in conflict with our previous reports (Wörgötter *et al.* 1998*b*), because in these studies we analysed the EEG dependence of the *phasic* RF width obtained within the first 20–30 ms of the response. In that case, we found that (in a normal cortex) phasic RFs are wider during synchronized as compared with less-synchronized EEG. The tonic RF width, however, remains the same, as reported here.

8. FUNCTIONAL SPECULATIONS

It was suspected in several earlier reports that the dLGN should be involved in 'smart' visual-gating processes (Sherman & Koch 1986; Sillito & Murphy 1988). Its location between the more machine-like operating retina and the sophisticated feature-analysing cortex indeed

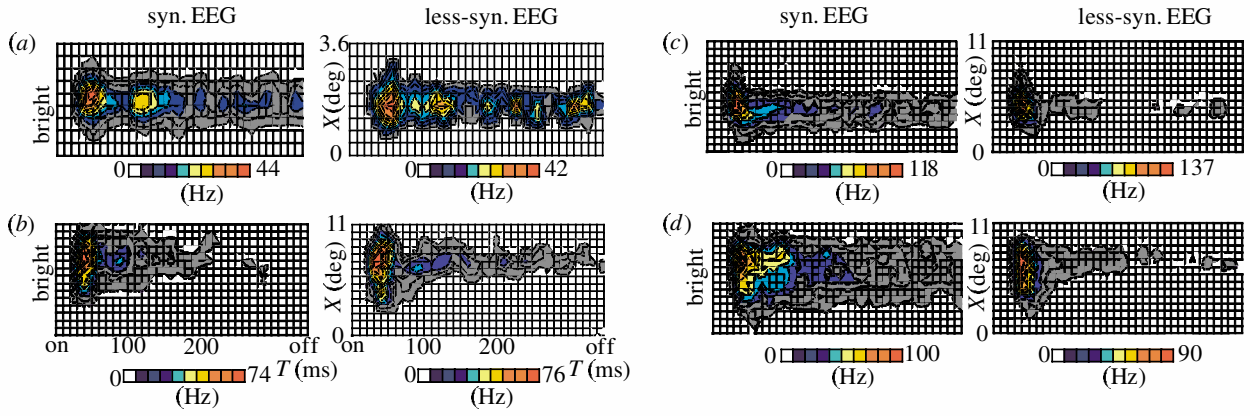

Figure 8. RF plots showing the results from induced apoptosis of the corticothalamic projection. Two representative neurons are depicted from control (*a*,*b*), and from experimental hemispheres (*c*,*d*). Visual stimuli were presented monocularly, as bright and dark bars (size: 0.2–0.8° × 3–6°; contrast 33 and −33%, respectively, displayed on a computer screen. Optimally sized and oriented bars were presented at 16 evenly spaced positions along a line cross-sectioning the RF-centre, in a pseudo-random sequence. The two extreme presentation positions extended beyond the RF borders. Each stimulus was shown with a duty-cycle of 350 ms presentation time and 150 ms pause. Neurons from the control and the experimental hemispheres were stimulated in an interleaved manner, for a total duration of 20–60 min, depending on the general responsiveness of the neurons. The pseudo-coloured images show how the activity of each cortical neuron across the centre of its RFs develops over time. Responses in control hemispheres (*a*,*b*) are longer and more pronounced during less-synchronized EEG. The situation is reversed in the experimental hemispheres (*c*,*d*), where responses are stronger and have a longer duration during synchronized EEG. (Modified from Eyding *et al.* 2002.)

makes the dLGN an ideal candidate for this type of operation. Its responses are still rather similar to those in the retina which allows for faithful information transmission as would be required by a 'gate'; however, the dLGN receives a variety of non-retinal inputs which could well support different 'gating outcomes'. Table 1 summarizes the main findings comparing EEG-related effects with those obtained by inactivation of the corticothalamic projection.

Consistently one finds that the temporal and spatial specificity in dLGN and cortex is lower during synchronized EEG than during less-synchronized EEG (compare EEG states in the 'normal' section of table 1).

Another central observation is that chronic inactivation of the corticothalamic feedback affects the cortical (and dLGN, not shown) responses mainly during *synchronized* EEG leading to an *enhancement* of response amplitude and duration whereas acute inactivation affects mainly dLGN responses during less-*synchronized* EEG leading to an *attenuation*. We interpret the enhancement after chronic inactivation in terms of a plasticity reaction of the cortical (and possible also dLGN) network, which probably tries to compensate for the cell loss in the cortex. The rather long period between cell-death induction and concluded apoptosis (10–14 days) certainly leads to restructuring effects within the remaining network. Similar effects have been reported in the cortex and dLGN after retinal de-afferentation (Eysel 1979; Eysel & Schweigart 1999). In these experiments a response-enhancing compensatory plasticity reaction has been observed, which was even more pronounced than that shown here. Corticothalamic cells are excitatory; thus, it seems that after removal of these projections the remaining network tries to counterbalance the resulting reduced excitation, possibly by an unspecific facilitatory effect, which raises the net excitability within the network and may be based on supersensitivity to the remaining excitatory inputs, or a reduced tonic inhibition. This effect seems to be subtle and may therefore only become visible during synchronized EEG where the activity level is normally lower—such that changes become more easily noticeable—than during less-synchronized EEG. The similarity of effects observed in the dLGN after apoptosis argues against a strong intracortical origin for the effects originating from the equally disrupted layer 6-to-4 collateral system. These connections are excitatory, but it is suspected that they are mainly involved in recurrent intracortical loops (Stratford *et al.* 1996), where they could, through secondary connection, in principle also lead to an inhibitory effect. Thus, some effects, for example the covariation of response amplitude with RF size in the treated cases, could indeed be related to a loss of (lateral) inhibition resulting from a loss of 6-to-4 collaterals. This is supported by results that have shown that the lower layer can provide an inhibitory input to the upper layers (Bolz & Gilbert 1986; Allison *et al.* 1995). Retinal de-afferentation, however, leads to a more substantial reduction of excitation and, as a consequence, the compensatory plasticity reaction is more pronounced. While these speculations need further (e.g. histological) support, we believe nonetheless that their inner consistency indicates that they are, in general, valid.

The summary of the observations given in table 1 also clearly indicates that the dLGN normally operates within a very finely balanced regime of excitation and inhibition. Small changes in the depolarization level at a dLGN relay cell can lead to a rather strongly changed behaviour. Curro Dossi *et al.* (1992) have shown that a hyperpolarization of only 9 mV is enough to push dLGN cells into burst-firing mode (Llinás & Jahnsen 1982). An increase in burst firing and lack of tonic behaviour is also the most dominant effect during extensive cortical inactivation (Kalil & Chase 1970; Funke & Eysel 1992). This indicates that the membrane potential at the observed dLGN cells has substantially dropped as shown by intracellular studies (Curro

Table 1. Summary of the main effects that occur during an EEG change as compared with those obtained during chronic or acute inactivation of the corticothalamic feedback.

		normal		*feedback chronically inactivated*	
cortex		synchronized EEG	less-synchronized EEG	synchronized EEG	less-synchronized EEG
	tonic amplitude	low	high	substantially increased	no change
	temporal properties	phasic	tonic	substantially less phasic	no change
	spatial properties	early RF wide	early RF narrow	no change	no change
		late (tonic) RF similar		late RF substantially wider	no change
			summary:	*enhancement*	no change
		normal		*feedback acutely inactivated*	
dLGN		synchronized EEG	less-synchronized EEG	synchronized EEG	less-synchronized EEG
	tonic amplitude	(very) low	high	no change	substantially reduced
	temporal properties	phasic	tonic	no change	more phasic
		narrow (sharp) multi-peak INTH with dominant higher-order peaks	narrow (sharp) multi-peak INTH with dominant fundamental peak	no change	dispersed multi-peak INTH with dominant higher-order peaks; reduced synchronicity
	spatial properties	only indistinct differences observed		no change	
			summary:	no change	*reduction*

Dossi *et al.* 1992). More subtle inactivation of the cortex by less intense cooling or by GABA micro-iontophoresis into the cortex leaves the dLGN cell in the tonic firing mode but firing now occurs with longer intervals between spikes (see figure 4); in addition, spikes are now more dispersed in time. This indicates that the active cortex sharpens the temporal firing pattern, possibly leading to a higher temporal accuracy in signal transmission (synchronization; Sillito *et al.* 1994; Kirkland *et al.* 2000), affecting the spatio-temporal response properties and the amount of information transmitted from the dLGN to the cortex (McClurkin *et al.* 1994; Marrocco *et al.* 1996).

Gradually these observations lead to a more unequivocal interpretation of the action of the corticothalamic feedback in experimental, anaesthetized conditions. The situation, however, is less clear during normal, awake, physiological states without experimental interference. It seems, however, fair to assume that 'in normal life' the cortex also acts mainly in a facilitatory manner onto the dLGN. In addition, the discussion should not overlook the closed-loop aspect: the corticothalamic influence will, within a single loop, re-enter the cortex and also lead to an altered behaviour there (Wörgötter *et al.* 1998*b*; Hillenbrand & van Hemmen 2000). The results from chronic inactivation, which certainly relate more strongly to plasticity effects, nevertheless clearly indicate that the influence of the corticothalamic loop does not end at the dLGN, but that it also influences the cortex through closing the loop. Furthermore, one can reasonably assume that the action of the corticothalamic feedback will be more localized in a physiological situation leading to locally different influences on the dLGN. We would also expect that it is subtler, as compared with the rather coarse effect of experimental cortical inactivation.

As a consequence, in an awake, physiological situation such subtle shifts in corticothalamic activity would most probably lead to a locally changed *efficiency* and *accuracy* in signal transmission. It has been speculated that this could be used by the system to locally control the (spatial and temporal) visual resolution (Desimone & Duncan 1995; Posner & Gilbert 1999; Suder & Wörgötter 2000; Deco & Zihl 2001). Studies of visual attention clearly indicate that such mechanisms could indeed exist. Focal attention improves spatial resolution (Yeshurun & Carrasco 1998) and favours the detection of fine details while spread attention facilitates the detection of large-scale objects (Balz & Hock 1997; Hock *et al.* 1998). This is also the reason why we perceive a bar flashed within the focus of our attention to be shorter (smaller) than when it is flashed at a position outside the current focus of attention (Tsal & Shalev 1996). This could be indicative of a physiological mechanism that enhances the detection of changes in the visual field outside our focus of attention by enhanced 'effective connectivity/convergence' but improves spatial resolution as soon as the object is captured by the focus of attention. The corticothalamic projection could contribute to this process in a way already described above: by enhancing spatial brightness and fea-

ture contrast in the dLGN via a centre–surround organization of local gain control. Focal changes in activity topographically correlated to shifts of the 'spotlight' of visual attention have been demonstrated for human primary visual cortex (Brefczynski & DeYoe 1999; Somers *et al.* 1999). It is thus reasonable to assume that even the first-order sensory nuclei of the thalamus are involved in processes controlling the spatial scale of attention (Crick 1984; Sherman & Koch 1986; Sherman & Guillery 2001); however, ultimate physiological evidence for such a mechanism is still missing (for example, Bender & Youakim 2001; Sary *et al.* 2001).

Changes in the temporal resolution of dLGN responses are especially observed during a transition between an awake(-like) and a sleep(-like) state of the individual. While bursts dominate during sleep, more tonic responses are found in the awake state (Weyand *et al.* 2001). Bursts could mainly serve as a wake-up signal, whereas tonic responses allow for a faithful encoding of diverse stimulus parameters (but see Reinagel *et al.* 1999; Funke & Kerscher 2000). In addition, synchronization processes, which are possibly involved in the encoding of more complex relations between stimuli, rely heavily on tonic activity. Bursts are too short to allow for any synchronization to take place. It also seems probable that in a physiological state an active corticothalamic feedback shifts the dLGN activity patterns further into tonic states, facilitating such processes.

In summary, this shows that the dLGN operates in different modes depending on a rather finely tuned balance between excitation and inhibition arriving at the individual cells. While the physiological results have become increasingly lucid in recent years, functional interpretations are still, to a large degree, speculative. However, due to the detailed physiological understanding, we are approaching a position of being able to design very detailed biophysical models of the retina (Hennig *et al.* 2002) and dLGN (Einevoll & Heggelund 2000; Ruksenas *et al.* 2000) which will probably help to clarify functional issues in an interplay with novel physiological experiments.

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APPENDIX A: SUMMARY OF METHODS

The methods applied to obtain the results shown in this article have been reported in detail in several original publications (Li *et al.* 1999; Wörgötter *et al.* 1998*a*,*b*) and, therefore, we will only provide a summary here. In the following, we will briefly describe the complete procedure which was applied to induce specific cell death of the corticothalamic projection neurons (Macklis 1993; Sheen & Macklis 1995; Magavi *et al.* 2000; Scharff *et al.* 2000; Shin *et al.* 2000) and the physiological experiments performed thereafter. Experimental procedures were similar in the other experiments and we will, at the end of this section, indicate some of the more important differences.

(a) *General procedures*

All experiments were performed in adult cats. Initial surgery was performed under deep anaesthesia with a combination of ketamine (25 mg kg^{-1}) and xylazine (1 mg kg^{-1}) and craniotomies were performed to allow access to the dLGN and cortex. All incisions were also locally anaesthetized by xylocaine. These methods are in accordance with the German laws of animal welfare and were approved by the local animal welfare committee.

(b) *Inducing cell death*

Latex nanospheres carrying the targeting chromophore chlorin e_6 were stereotaxically injected into both layers A and A_1 of the dLGN of one hemisphere under RF-position control. After 2–3 weeks, allowing sufficient time for retrograde transport of the photoactive nanospheres, apoptosis of corticothalamic neurons was induced in cortical layer 6 of primary visual cortex areas 17/18. Neuronal apoptosis was induced via the non-invasive, transdural activation of chlorin e_6 with 674 nm light delivered by a continuous-wave laser. Light was applied after exposing the appropriate cortical surface representing the same visual field position as the injection sites. Following light exposure, neuronal apoptosis progressively developed over 10–14 days.

(c) *Recordings*

After this time we applied conventional approaches for semi-acute extracellular recording, to allow RF mapping (Wörgötter *et al.* 1998*b*). Data were obtained by single-unit recordings, using glass micropipettes in cortical areas 17/18, or the dLGN. Visual stimuli were presented monocularly and will be described when presenting the results.

(d) *EEG analysis*

The state of the EEG was determined by a 'sliding-window' fast Fourier transformation of the EEG trace and the calculation of the δ-power ratio (power of 1–4 Hz-band/all bands). Files were separated into less-synchronized (less-syn.) and synchronized (syn.) episodes, using a threshold power ratio of 0.5 (method slightly modified from Li *et al.* 1999). 'Less-synchronized' in the anaesthetized animal is that particular state that most closely resembles a desynchronized EEG in awake animals.

(e) *Analysis of single unit activity*

Several methods have been used to analyse neuronal responses. dLGN responses have been analysed using intervalograms (see Funke & Wörgötter 1995) which essentially represent a sliding-window INTH. Here we will, however, only show cross-sections through such intervalograms that correspond to conventional temporally localized INTHs. Cortical responses are represented as contour maps derived from a 3D plot with time and space as the *x*- and *y*-axes, and impulse rate colour coded. Such contour plots were smoothed with a spatial low pass and spontaneous activity was subtracted. Several width and duration measures were obtained from these contour plots, which are used to quantify changes in the RF structure.

(f) *Histology*

Standard methods were used to obtain histological sections of the experimentally treated dLGNs and cortices prepared for fluorescence microscopy or cresyl-violet staining (Nissl stain). Sections from the regions of targeted neuronal apoptosis and the homologous regions of the control hemispheres were processed for immunocytochemistry necessary to allow for cell counting.

(g) *Cell counting*

Complex counting procedures were applied using modified, semi-automatic, stereological methods (Guillery & Herrup 1997), to quantify neuronal population density in experimental versus control regions of cortical areas 17/18. Methods were based on NeuN-labelling applying nickel-enhanced DAB (DAB-Ni) staining for NeuN. Counting was performed in matched 'regions of interest' and cell profiles were aligned with respect to the transition between layers 5A and 5B where a strong drop of cell density exists, which can be used as a distinct feature for accurate alignment.

(h) *Control experiments*

In general, all experimental procedures were held against controls. In standard experiments, classical 'control' versus 'recovery' controls were made. In the more critical cell death studies, one sham-control experiment was performed, specifically to test our procedures for inducing targeted neuronal apoptosis, in which all experimental steps were completed except for initiation of targeted neuronal death. We found no changes in cortical histology and no change in any electrophysiological parameter, compared with intact controls. In those experiments where apoptosis was performed, we always measured the cell activity simultaneously in both the treated, and the untreated, hemisphere. Recordings from the untreated hemisphere, thereby, also serve as a control.

Furthermore, in two cats, we performed control measurements in the dLGN ($n = 36$ neurons) after induction of apoptosis, in order to reproduce the previously published effects of elimination of EEG dependence of the tonic response component (Funke & Eysel 1992) and loss of temporal precision of the intervals of that tonic component (Wörgötter *et al.* 1998*a*).

(i) *Micro-iontophoresis*

Micro-iontophoresis was performed in the dLGN using multi-barrel pipettes. Depending on the experimental set-up, the micro-iontophoresis barrels were filled with GABA (0.5 M, pH 3.0, saline) or BICU (5 mM, pH 3.0, saline).

(j) *Cortical inactivation*

This was achieved by two methods: cortical cooling and bulk GABA micro-iontophoresis. Cooling was performed by attaching an open (pressure-free) cooling chamber to the skull above areas 17 and 18 with a cooling liquid (Ringer solution) at 0 °C. To inactivate a large area of the cortex by GABA micro-iontophoresis a square array of 4×4 micropipettes was inserted into the infragranular layers of cortical areas 17 and 18. The lateral distance between two tips was *ca.* 1000 μm. All pipettes were filled with GABA and attached in parallel in bundles of four to the channels of the neurophore control unit.

REFERENCES

Allison, J. D., Casagrande, V. A. & Bonds, A. B. 1995 The influence of input from the lower cortical layers on the orientation tuning of upper layer V1 cells in a primate. *Vis. Neurosci.* **12**, 309–320.

Baker, F. H. & Malpeli, J. G. 1977 Effects of cryogenic blockade of visual cortex on the responses of lateral geniculate neurons in the monkey. *Exp. Brain Res.* **29**, 433–444.

Balz, G. W. & Hock, H. S. 1997 The effect of attentional spread on spatial resolution. *Vis. Res.* **37**, 1499–1510.

Bolz, J. & Gilbert, C. D. 1986 Generation of end-inhibition in the visual cortex via interlaminar connections. *Nature* **320**, 362–365.

Bender, D. B. & Youakim, M. 2001 Effect of attentive fixation in macaque thalamus and cortex. *J. Neurophysiol.* **85**, 219–234.

Brefczynski, J. A. & DeYoe, E. A. 1999 A physiological correlate of the 'spotlight' of visual attention. *Nature Neurosci.* **2**, 370–374.

Contreras, D. & Steriade, M. 1996 Spindle oscillation in cats: the role of corticothalamic feedback in a thalamically generated rhythm. *J. Physiol. (Lond.)* **490**, 159–179.

Contreras, D., Destexhe, A., Sejnowski, T. J. & Steriade, M. 1997 Spatiotemporal patterns of spindle oscillations in cortex and thalamus. *J. Neurosci.* **17**, 1179–1196.

Crick, F. 1984 Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl Acad. Sci. USA* **81**, 4586–4590.

Cudeiro, J. & Sillito, A. M. 1996 Spatial frequency tuning of orientation-discontinuity-sensitive corticofugal feedback to the cat lateral geniculate nucleus. *J. Physiol. (Lond.)* **490**, 481–492.

Cudeiro, J., Rivadulla, C. & Grieve, K. L. 2000 Visual response augmentation in cat (and macaque) LGN: potentiation by corticofugally mediated gain control in the temporal domain. *Eur. J. Neurosci.* **12**, 1135–1144.

Curro Dossi, R., Nunez, A. & Steriade, M. 1992 Electrophysiology of a slow (0.5–4 Hz) intrinsic oscillation of cat thalamocortical neurones *in vivo*. *J. Physiol. (Lond.)* **447**, 215–234.

Deco, G. & Zihl, J. 2001 A neurodynamical model of visual attention: feedback enhancement of spatial resolution in a hierarchical system. *J. Comp. Neurosci.* **10**, 231–253.

Desimone, R. & Duncan, J. 1995 Neural mechanisms of selective visual attention. *A. Rev. Neurosci.* **18**, 193–222.

Einevoll, G. T. & Heggelund, P. 2000 Mathematical models for the spatial receptive-field organization of non-lagged X-cells in the dorsal lateral geniculate nucleus of cat. *Vis. Neurosci.* **17**, 871–885.

Eyding, D., Macklis, J. D., Neubacher, U., Funke, K. & Wörgötter, F. 2002 Selective elimination of cortico-thalamic feedback abolishes the EEG dependence of primary visual cortical receptive fields and reduces their spatial specificity. *J. Neurosci.* (Submitted.)

Eysel, U. T. 1979 Maintained activity, excitation and inhibition of lateral geniculate neurons after monocular deafferentation in the adult cat. *Brain Res.* **166**, 259–271.

Eysel, U. T. & Schweigart, G. 1999 Increased receptive field size in the surround of chronic lesions in the adult cat visual cortex. *Cerebr. Cortex* **9**, 1047–3211.

Funke, K. & Eysel, U. T. 1992 EEG-dependent modulation of response dynamics of cat dLGN relay cells and the contribution of the corticogeniculate feedback. *Brain Res.* **573**, 217–227.

Funke, K. & Kerscher, N. 2000 High-frequency (300–800 Hz) components in cat geniculate (dLGN) early visual responses. *J. Physiol. (Paris)* **94**, 411–425.

Funke, K. & Wörgötter, F. 1995 Temporal structure in the

light response of relay cells in the dorsal lateral geniculate nucleus of the cat. *J. Physiol. (Lond.)* **485**, 715–737.
Funke, K. & Wörgötter, F. 1997 On the significance of temporally structured activity in the dorsal lateral geniculate nucleus (LGN). *Prog. Neurobiol.* **53**, 67–119.
Guillery, R. W. & Herrup, K. 1997 Quantification without pontification: choosing a method for counting objects in sectioned tissues. *J. Comp. Neurol.* **386**, 2–7.
Hennig, M., Funke, K. & Wörgötter, F. 2002 The influence of different retinal sub-circuits on the non-linearity of ganglion cell behavior. *J. Neurosci.* **22**, 8726–8738.
Hillenbrand, U. & van Hemmen, J. L. 2000 Spatiotemporal adaptation through corticothalamic loops: a hypothesis. *Vis. Neurosci.* **17**, 107–118.
Hock, H. S., Balz, G. W. & Smollen, W. 1998 Attentional control of spatial scale: effects on self-organized motion patterns. *Vis. Res.* **38**, 3743–3758.
Ikeda, H. & Wright, M. J. 1974 Sensitivity of neurones in visual cortex (area 17) under different levels of anaesthesia. *Exp. Brain Res.* **20**, 471–484.
Kalil, R. E. & Chase, R. 1970 Corticofugal influence on activity of lateral geniculate neurons in the cat. *J. Neurophysiol.* **33**, 459–474.
Kirkland, K. L., Sillito, A. M., Jones, H. E., West, D. C. & Gerstein, G. L. 2000 Oscillations and long-lasting correlations in a model of the lateral geniculate nucleus and visual cortex. *J. Neurophysiol.* **84**, 1863–1868.
Li, B., Funke, K., Wörgötter, F. & Eysel, U. T. 1999 Correlated variations in EEG pattern and visual responsiveness of cat lateral geniculate relay cells. *J. Physiol. (Lond.)* **514**, 857–874.
Livingstone, M. S. & Hubel, D. H. 1981 Effects of sleep and arousal on the processing of visual information in the cat. *Nature* **291**, 554–561.
Llinás, R. & Jahnsen, H. 1982 Electrophysiology of mammalian thalamic neurons *in vitro*. *Nature* **297**, 406–408.
McClurkin, J. W. & Marrocco, R. T. 1984 Visual cortical input alters spatial tuning in monkey lateral geniculate nucleus cells. *J. Physiol. (Lond.)* **348**, 135–152.
McClurkin, J. W., Optican, L. M. & Richmond, B. J. 1994 Cortical feedback increases visual information transmitted by monkey parvocellular lateral geniculate nucleus neurons. *Vis. Neurosci.* **11**, 601–617.
McCormick, D. A. & Von Krosigk, M. 1992 Corticothalamic activation modulates thalamic firing through glutamate 'metabotropic' receptors. *Proc. Natl Acad. Sci. USA* **89**, 2774–2778.
Macklis, J. D. 1993 Transplanted neocortical neurons migrate selectively into regions of neuronal degeneration produced by chromophore-targeted laser photolysis. *J. Neurosci.* **13**, 3848–3863.
Magavi, S. S., Leavitt, B. R. & Macklis, J. D. 2000 Induction of neurogenesis in the neocortex of adult mice. *Nature* **405**, 951–955.
Marrocco, R. T., McClurkin, J. W. & Alkire, M. T. 1996 The influence of the visual cortex on the spatiotemporal response properties of lateral geniculate nucleus cells. *Brain Res.* **737**, 110–118.
Murphy, P. C. & Sillito, A. M. 1987 Corticofugal feedback influences the generation of length tuning in the visual pathway. *Nature* **329**, 727–729.
Murphy, P. C. & Sillito, A. M. 1996 Functional morphology of the feedback pathway from area 17 of the cat visual cortex to the lateral geniculate nucleus. *J. Neurosci.* **16**, 1180–1192.
Murphy, P. C., Duckett, S. G. & Sillito, A. M. 2000 Comparison of the laminar distribution of input from areas 17 and 18 of the visual cortex to the lateral geniculate nucleus of the cat. *J. Neurosci.* **20**, 845–853.
Posner, M. I. & Gilbert, C. D. 1999 Attention and primary visual cortex. *Proc. Natl Acad. Sci. USA* **96**, 2585–2587.
Reinagel, P., Godwin, D., Sherman, S. M. & Koch, C. 1999 Encoding of visual information by LGN bursts. *J. Neurophysiol.* **81**, 2558–2569.
Rivadulla, C., Martinez, L. M., Varela, C. & Cudeiro, J. 2002 Completing the corticofugal loop: a visual role for the corticogeniculate type I metabotropic glutamate receptor. *J. Neurosci.* **22**, 2956–2962.
Ruksenas, O., Fjeld, I. T. & Heggelund, P. 2000 Spatial summation and centre-surround antagonism in the receptive field of single units in the dorsal lateral geniculate nucleus of cat: comparison with retinal input. *Vis. Neurosci.* **17**, 855–870.
Sary, G., Xu, X., Shostak, Y., Schall, J. & Casagrande, V. 2001 Extraretinal modulation of cells in the lateral geniculate nucleus (LGN). *Soc. Neurosci. Abstr.* 723.15.
Sawai, H., Morigiwa, K. & Fukuda, Y. 1988 Effects of EEG synchronization on visual responses of cat's geniculate relay cells: a comparison among Y, X and W cells. *Brain Res.* **455**, 394–400.
Scharff, C., Kirn, J., Grossman, M., Macklis, J. D. & Nottebohm, F. 2000 Targeted neuronal death affects neuronal replacement and vocal behavior in adult songbirds. *Neuron* **25**, 481–492.
Scharfman, H. E., Lu, S. M., Guido, W., Adams, P. R. & Sherman, S. M. 1990 *N*-methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. *Proc. Natl Acad. Sci. USA* **87**, 4548–4552.
Sheen, V. L. & Macklis, J. D. 1995 Targeted neocortical neuron cell death in adult mice guides migration and differentiation of transplanted embryonic neurons. *J. Neurosci.* **15**, 8378–8392.
Sherman, S. M. & Koch, C. 1986 The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. *Exp. Brain Res.* **63**, 1–20.
Sherman, S. M. & Guillery, R. W. 2001 *Exploring the thalamus*. San Diego, CA: Academic Press.
Shin, J. J., Fricker-Gates, R. A., Perez, F. A., Leavitt, B. R., Zurakowski, D. & Macklis, J. D. 2000 Transplanted neuroblasts differentiate appropriately into projection neurons with the correct neurotransmitter and receptor phenotype in neocortex undergoing targeted projection neuron neurodegeneration. *J. Neurosci.* **20**, 7404–7416.
Sillito, A. M. & Murphy, P. C. 1988 The modulation of the retinal relay to the cortex in the dorsal lateral geniculate nucleus. *Eye Suppl.* **2**, 221–232.
Sillito, A. M., Cudeiro, J. & Murphy, P. C. 1993 Orientation sensitive elements in the corticofugal influence on centre-surround interactions in the dorsal lateral geniculate nucleus. *Exp. Brain Res.* **93**, 6–16.
Sillito, A. M., Jones, H., Gerstein, G. L. & West, D. C. 1994 Feature-linked synchronisation of thalamic relay cell firing induced by feedback from the visual cortex. *Nature* **369**, 479–482.
Sillito, A. M., Grieve, K., Jones, H., Cudeiro, J. & Davis, J. 1995 Visual cortical mechanisms detecting focal orientation discontinuities. *Nature* **378**, 492–496.
Singer, W. 1977 Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. *Physiol. Rev.* **57**, 386–420.
Singer, W., Tretter, F. & Cynader, M. 1976 The effect of reticular stimulation on spontaneous and evoked activity in the cat visual cortex. *Brain Res.* **102**, 71–90.
Somers, D. C., Dale, A. M., Seiffert, A. E. & Tootell, R. B. H. 1999 Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Neurobiology* **96**, 1663–1668.

Steriade, M. 1997 Synchronised activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cerebr. Cortex* **7**, 583–604.

Stratford, K. J., Tarczy-Hornoch, K., Martin, K. A. C., Bannister, N. J. & Jack, J. J. B. 1996 Excitatory synaptic inputs to spiny stellate cells in cat visual cortex. *Nature* **382**, 258–261.

Suder, K. & Wörgötter, F. 2000 The control of low-level information flow in the visual system. *Rev. Neurosci.* **11**, 127–146.

Tsal, Y. & Shalev, L. 1996 Inattention magnifies perceived length: the attentional receptive field hypothesis. *J. Exp. Psychol.* **22**, 233–243.

Tsumoto, T., Creutzfeldt, O. D. & Legendy, C. R. 1978 Functional organisation of the cortifugal system from visual cortex to lateral geniculate nucleus in the cat. With an appendix on geniculo-cortical mono-synaptic connections. *Exp. Brain Res.* **32**, 345–364.

Vidyasagar, T. R. & Urbas, J. V. 1982 Orientation sensitivity of cat LGN neurones with and without inputs from visual cortical areas 17 and 18. *Exp. Brain Res.* **46**, 157–169.

Weber, A. J., Kalil, R. E. & Behan, M. 1989 Synaptic connections between corticogeniculate axons and interneurons in the dorsal lateral geniculate nucleus of the cat. *J. Comp. Neurol.* **289**, 156–164.

Weyand, T. G., Boudreaux, M. & Guido, W. 2001 Burst and tonic response modes in thalamic neurons during sleep and wakefulness. *J. Neurophysiol.* **85**, 1107–1118.

Wörgötter, F., Nelle, E., Li, B. & Funke, K. 1998*a* The influence of corticofugal feedback on the temporal structure of visual responses of cat thalamic relay cells. *J. Physiol.* (*Lond.*) **509**, 797–815.

Wörgötter, F., Suder, K., Zhao, Y., Kerscher, N., Eysel, U. T. & Funke, K. 1998*b* State-dependent receptive-field restructuring in the visual cortex. *Nature* **396**, 165–168.

Wörgötter, F., Suder, K. & Funke, K. 1999 The dynamic spatio-temporal behaviour of visual responses in thalamus and cortex. *Rest Neurol. Neurosci.* **15**, 137–152.

Yeshurun, Y. & Carrasco, M. 1998 Attention improves or impairs visual performance by enhancing spatial resolution. *Nature* **395**, 72–75.

GLOSSARY

BICU: bicuculline methiodide
dLGN: dorsal lateral geniculate nucleus
EEG: electroencephalograph
GABA: γ-aminobutyric acid
INTH: interspike interval histogram
LGN: lateral geniculate nucleus
PSTH: peri-stimulus time histogram
RF: receptive field