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

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Summary: In this article we review results on the in vivo properties of neurones in the dorsal lateral geniculate nucleus (dLGN) which receives its afferent input from the retina and projects to the visual cortex. In addition, the dLGN gets 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 EEG (which are mainly related to a changing brain stem influence), with those that are obtained when experimentally silencing the corticothalamic feedback. 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, pointing to a hyperpolarizing effect. By means of a novel method we were able to chronically eliminate a large proportion of the corticothalamic projection neurones from the otherwise intact cortex. In this condition we found that cortical cells also lose their EEG specific response differences but this time probably due to a facilatory (depolarizing) plasticity reaction of the remaining network.

Key Index Words: Visual thalamus, state dependence, corticothalamic feedback, targeted cell death, gating processes.

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 dorsal lateral geniculate nucleus (dLGN) to the (primary) visual cortex and back consists of a massive bundle of fibres and provides about 50% of the synapses in the dLGN. Despite of its substantial size only relatively weak and non-uniform effects on the responses in dLGN cells have been reported of this projection. This may have to do with the fact that almost all experiments which address the action of the corticothalamic projection had to be performed either *in vitro* or in anaesthetised *in vivo* preparations. In addition, so far it had not been possible to record cortical cells during an inactive feedback loop, which might also provide more insight into the closed loop properties of this feedback system. The earliest experiments in which the corticothalamic projection was inactivated suggested a rather broad, unspecific

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facilatory action from 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 receptive fields (Vidyasagar & Urbas 1982; McClurkin & Marrokko 1984; Murphy & Sillito 1987; Sillito & Murphy 1988; Sillito et al. 1993, 1995; Cudeiro & Sillito 1996). It is likely that corticothalamic feedback is organised in an antagonistic "centre/surround" fashion – exerting a facilatory influence within a centre of topographic match (about 1 to 2 deg) but a suppressive effect from surrounding regions (Tsumoto et al. 1978). This may contribute to dLGN receptive field tuning but may also affect saliency of stimuli via focal changes in 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 support these processes, e.g. corticothalamic control of temporal synchronisation 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 has been 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 which is involved in the generation and synchronisation of fast (20-50 Hz) and slow (< 15 Hz) oscillations in thalamocortical networks, characterising activated (less-synchronised) 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 synchronisation of thalamically generated rhythms like 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 & 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 seems to be also 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 synchronisation (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 EEG pattern (Livingstone & Hubel 1981; Singer et al. 1976). This, however, also suggested that, in an experiment, effects induced by a change in the EEG can be easily 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 as that induced by silencing the cortex (Funke & Eysel 1992; Wörgötter et al. 1998a).

In this article we will therefore mainly review results which juxtapose EEG-related effects with those induced by inactivating the corticothalamic projection. Furthermore we will summarise results about 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.

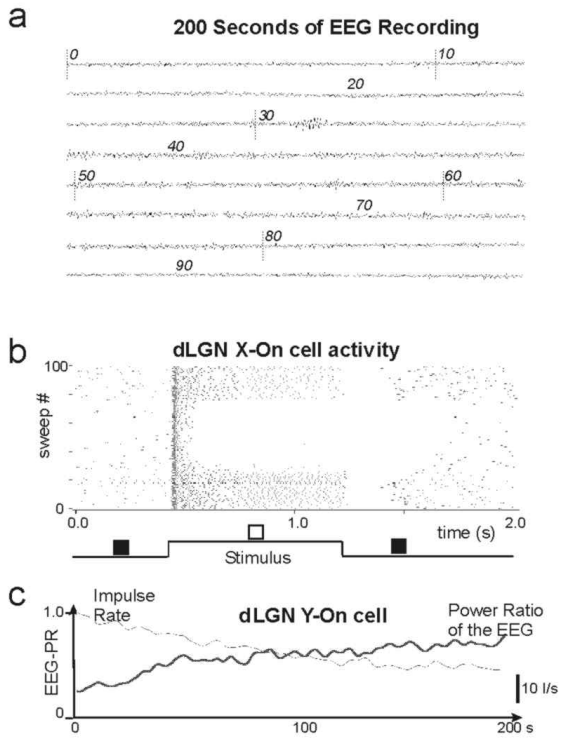

Fig. 1) Influence of the EEG-state on the neuronal responses in the dLGN. A) EEG-trace recorded for 200 s, showing pronounced δ-waves in the middle of the trace. Small numbers indicate the corresponding stimulus repetition ("sweep"). B) Dot raster diagram of an X-ON-cell response recorded simultaneously to the EEG-trace in (A). The stimulus (flashing bright spot, 1.0 deg., contrast 0.9) timing diagram is depicted on the bottom. The cell responds 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) stimulated also 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)

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 which is dominated by δ-waves (Livingston & Hubel 1981; Sawai et al. 1988; Funke & Eysel 1992; Li et al. 1999). This state is in a non-anaesthetised situation usually associated with deep sleep. Even in an anaesthetised preparation, strong spontaneous transitions between a δ-wave dominated (so called *synchronised EEG*) and an EEG of reduced δ-wave activity (so called *less-synchronised EEG*) can be observed. Therefore, we expected that during synchronised EEG net excitation at the dLGN cells should be reduced. Fig. 1a shows this effect for 200 seconds of ongoing recording of a dLGN cell during stimulation with a flashing dot (100 sweeps of 2 sec.

each). The EEG traces on top show that δ-waves are more pronounced between stimulus sweep 25 and 75 when tonic dLGN light responses disappeared (Fig. 1b). During the other sweeps a less-synchronised EEG was observed and the cell showed a more pronounce tonic firing pattern. In Fig. 1c 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 emphasise 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).

In an earlier report we had shown that dLGN cells have preferred "interval modes" for firing such that multi-peak INTHs are obtained for most cells when analysing their spike trains in a specific way (Funke & Wörgötter 1995). Thus, the transition between synchronised and less-synchronised EEG not only affects the tonic firing of the cells but it is also reflected in a changed interval mode pattern. This is exemplified in Fig. 2. The EEG traces reflect a continuous transition from a less-synchronised to a strongly synchronised EEG[2]. As expected activity decreases and, in addition, it is clearly evident that the fundamental (leftmost) interval mode decreases during increasingly synchronised EEG at the cost of relatively larger higher-order interval modes.

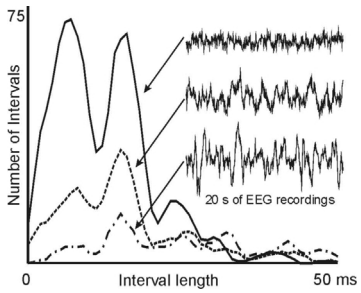

Fig. 2) Interspike interval histograms (INTHs) from an X-ON-cell stimulated with a flashing bright spot (2.0 deg., contrast 0.9, 100 sweeps, 2s each) recorded during different EEG states. Short traces of the corresponding EEG recording are shown in the insets. Multiple peaks are clearly visible in each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

Fig. 2 is not very well suited to demonstrate the tremendous impact that an EEG change can exert on the thalamic cell behaviour. Therefore, in Fig. 3 we show a few PSTHs of dLGN cells recorded during synchronised and less-synchronised EEG. The same cell changes its firing characteristic completely when such an EEG transition happens. During a less-synchronised EEG, the initial phasic response is followed by a pronounced tonic response component which is almost missing during synchronised EEG.

Reversible inactivation of the corticothalamic feedback

Fig. 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

[2] 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 and Wörgötter 1995).

rate of the tonic response as can be judged from the total number of spike in each recording (see figure legend). During recovery the cell almost re-obtains 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 of the (decreased) impulse rate of 10-15% between two subsequent recordings where quite common.

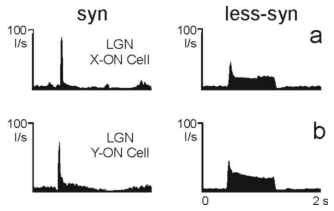

Fig. 3) Peri-stimulus time histograms (PSTHs) from an X-On (A) and a Y-On-cell (B) recorded during different EEG states. Both cells respond rather phasic during synchronized EEG and more tonic during less-synchronized EEG. Stimuli were: A) spot 0.3 deg. contrast 0.9, B) spot 1.0 deg. contrast 0.9 (modified from Wörgötter et al. 1998b).

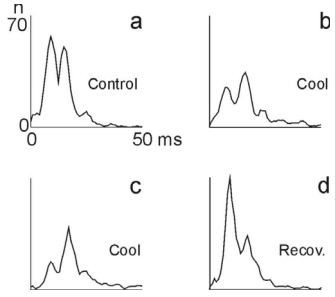

Fig. 4) Interspike interval histograms (INTHs) from an Y-On cell stimulated with a flashing bright spot (1.0 deg., contrast 0.9, 100 sweeps, 2s each) recorded during cortical cooling. The INTHs were obtained from a temporally localized cross-section through the corresponding intervalogram of these cell responses (see Fig. 2 in Wörgötter et al. 1998a). 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.

How to control for EEG-effects

The results shown 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 in the EEG is required in order to separate EEG-stages. In addition, we have in many cases performed double-unit recordings in the dLGN, where one recording site matched the cortical inactivation site whereas the other doesn't. This allowed us to distinguish 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 this to be good praxis in order to reliably unconfound effects.

Fig. 5 holds changes in mean impulse rate (x-axis) against EEG-changes (y-axis) for cells which match the inactivation side as compared to "non-matching" cells. The

results for non-matching cells centre on a mean of about 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 almost reduced by a factor of two as compared to the control group while the EEG stayed the same. The third smaller cluster on top shows 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. As opposed to the situation observed during cortical inactivation, we now find a clear co-variation of both parameters. In summary, Fig. 5 demonstrates that EEG effects can be clearly separated from the experimentally induced effects by this control method.

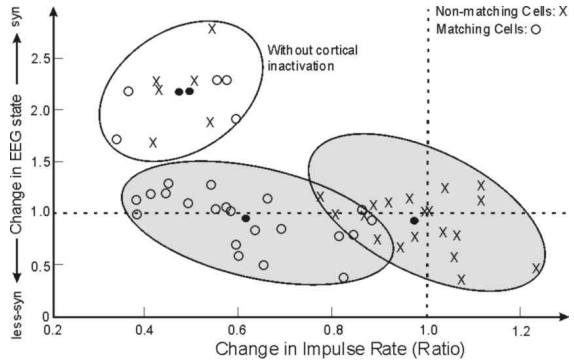

Fig. 5) EEG-changes compared to changes in mean impulse rate for dLGN cells recorded at a site which topographically matched the cortical inactivation site ("matching cells") as compared to a control group recorded simultaneously from a non-matching site. The EEG remained unchanged at a ratio of about 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 group of recording on top shows cells without cortical cooling but during a strongly increase in the low-frequency components in the EEG. Both parameters co-vary in these cases. (modified from Wörgötter et al. 1998a)

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 facilatory cortical influence (Fig. 6, S1, black connection). On the other hand, it is well known that part of the corticothalamic fibres terminate on inhibitory interneurones in the dLGN (Weber et al. 1989). Thus, activation of the outer neuron in a chain of two connected inhibitory interneurones (Fig. 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 been reported, too, for distinct stimulus situations (Sillito et al. 1993; Cudeiro & Sillito 1996), but facilatory 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 showed a similar behaviour. Fig. 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 deg. Following the control recording, a small amount of GABA was applied (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. 1998a). GABA application was then continued at the same level but in addition we applied bicuculline with increasing dosage (10-20 nA, c,d). As expected, the inhibitory GABA effect could be almost totally antagonised and the ejection current of BICU (20 nA) was adjusted such that an optimal antagonising effect was obtained. Recovery (e) showed that these effects are reversible. In the next step drug application was stopped and cortical cooling started. Two recordings are shown (f,g) which demonstrate the reduction of dLGN activity during cooling but also show that significant fluctuations in the total number "n" of spikes are observed even in subsequent records (f: n=6281, g: n=6795). As discussed above, the cooling effect is not as reliable as direct drug induced effects shown in (b-d).

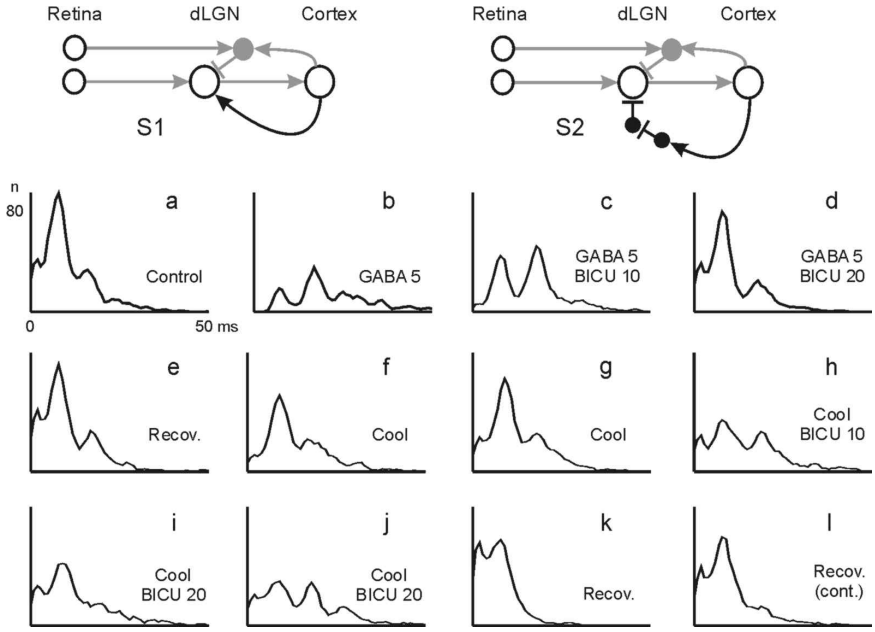

Fig. 6) Interaction of cortex inactivation with disinhibition of dLGN relay cells by BICU. Simplified connection scheme of the primary visual pathway showing the pathways for corticothalamic facilitation (S1) or disinhibition (S2) in black. Combination of cooling the cortex and micro-iontophoresis of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

If the cooling effect would be due to the inactivation of a disinhibitory circuit (e.g., Fig. 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 antagonise the cooling effect with BICU. Contrary to this assumption bicuculline did not antagonise the cooling effect (Fig. 6 h-j). This suggests that the facilatory effect of the corticothalamic feedback is predominantly mediated by direct excitatory connections (e.g., Fig. 6, S1) and not by disinhibition.

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 (Fig. 4). As an additional rather pronounced effect, however, we observed a widening of the interval peaks. Fig. 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 which 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 in a total of 69 cells that 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, on the other hand, made the peaks sharper in 46% of the cases (30% widening, 23% no-change).

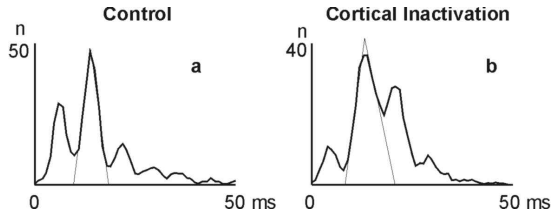

Fig. 7) Cortical inactivation leads to a broadening of the interval peaks in dLGN INTHs. X-ON-cell, stimulus: spot 1.5 deg., contrast 0.9. A) Control with sharp second INTH peak (see fitted straight lines), B) All peaks broaden during cortical inactivation by bulk GABA micro-iontophoresis (compare fitted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

The influence of the corticothalamic projection onto *cortical* cell responses

In this section we will describe 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 the Appendix; its goal is to allow for specifically eliminating a large proportion of the corticothalamic projection neurones without damaging other cells. Thereby we did arrive at a situation where the corticothalamic feedback is chronically removed from within an otherwise intact cortical network. This gave us the unique opportunity to record from cortical cell (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 this cell population had vanished after about 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 recorded from the remaining cortical neurons and to 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 particularly the temporal response properties of cortical neurons 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 brain stem activity, but it has been hypothesised that they are also

influenced by changes in corticothalamic activity (Funke & Eysel 1992, Wörgötter et al. 1998a).

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 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 EEG state. In control cortex with intact corticothalamic feedback circuitry, longer and more pronounced tonic responses occur during less-synchronised EEG states, as compared to shorter, more phasic responses during synchronised EEG (δ-wave dominated EEG). Fig. 8 a,b shows two examples of this quite typical behaviour. The diagrams show spatio-temporal receptive field plots of the activity of the control neurons recorded at the central cross-section through their receptive fields. In comparison, the right side (Fig. 8 c,d) shows two simultaneously recorded neurons from the experimentally treated hemisphere. In contrast to responses of neurons in control cortex, tonic responses in experimental cortex during synchronised EEG were significantly increased; in some cases they even exceeded responses observed during less-synchronised EEG, in duration and/or amplitude. Statistical analysis showed that tonic responses became on average 77±14% stronger and 64±10% longer compared to control during episodes of synchronised EEG. 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 synchronised EEG, while no changes where observed during less-synchronised EEG. In addition we found that non-specific neuronal electrophysiological characteristics, including spontaneous activity, remained unchanged.

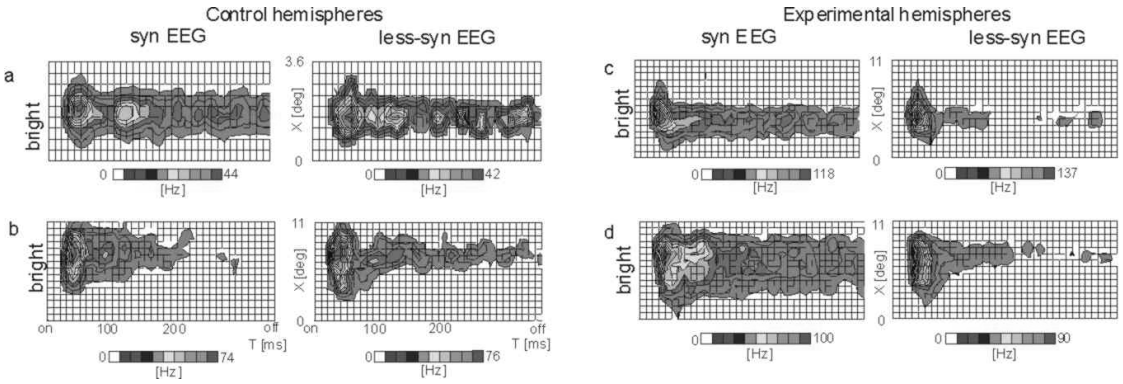

Fig. 8) Receptive field plots showing the results from induced apoptosis of the corticothalamic projection. Two representative neurons are depicted from control (a,b), and from experimental hemispheres (c,d). Visual stimuli were presented monocularly, as bright and dark bars (size: 0.2-0.8 deg x 3-6 deg; contrast $(100 \cdot (I-I_0)/(I+I_0))$ 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-center, 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 to 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 receptive fields develops over time. Responses in control hemispheres (a,b) are longer and more pronounced during less-synchronised EEG. The situation is reversed in the experimental hemispheres (c,d), where responses are stronger and have a longer duration during synchronised EEG. (modified from Eyding et al. 2002)

A second more subtle effect was also revealed through statistical analysis. We found a co-variation 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 receptive field (RF) remains constant in both EEG states, irrespective of the higher amplitude during less synchronised 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). Also in the LGN we found that the normally observed EEG-related differences between responses measured during synchronized- as compared to less-synchronized EEG vanish in the experimental animals. Similar to the cortical results also 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 older reports (Wörgötter et al. 1998b). Because in these studies we had analysed the EEG-dependence of the *phasic* receptive field width obtained within the first 20-30 ms of the response. There we found that (in a normal cortex) phasic RFs are wider during synchronised- as compared to less-synchronised EEG. The *tonic* RF width, however, stays the same as reported here.

Functional Speculations

It has been suspected in several older 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 makes the dLGN indeed 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”; on the other hand the dLGN receives a variety of non-retinal inputs which could well support different “gating outcomes”. Table 1 summarises the main findings comparing EEG-related effects with those obtained by inactivating the corticothalamic projection.

Consistently one finds that the temporal and spatial specificity in dLGN and cortex is lower during synchronised EEG than during less-synchronised EEG (Compare EEG states in the “Normal” section of the Table).

Another central observation is that chronic inactivation of the corticothalamic feedback affects the cortical (and dLGN, not shown) responses mainly during *synchronised* EEG leading to an *enhancement* of response amplitude and duration whereas acute inactivation affects mainly dLGN responses during *less-synchronised* 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 (10-14d) certainly

leads to restructuring effects within the remaining network. Similar effects have been reported in cortex and dLGN after retinal de-afferentation (Eysel 1979; Eysel & Schweigart 1999). Also 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 networks tries to counterbalance the resulting reduced excitation possibly by an unspecific facilatory effect which raises the net excitability within the network which may be based on super-sensitivity to the remaining excitatory inputs or a reduced tonic inhibition. This effect seems to be subtle and may therefore only become visible during synchronised EEG where the activity level is normally lower – such that changes become more easily noticeable – than during less-synchronised EEG. The similarity of effects observed in the dLGN after apoptosis argues against a strong intracortical origin of 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 inhibitory effect. Thus, some effects; for example the co-variation 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 6-4-collaterals. This is supported by results which have shown that the lower layer can provide inhibitory input to the upper layers (Bolz and Gilbert 1986, Allision et al 1995). Retinal de-afferentation, on the other hand, 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 in a very finely balanced regime of excitation and inhibition. Small changes in the depolarisation level at a dLGN relay cell can lead to a rather strongly changed behaviour. Curro Dossi et al. (1992) have shown that a hyperpolarisation of only 9 mV is enough to push dLGN cells into burst-firing mode (Llinás & Jahnsen 1982). 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 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 occurs now with longer intervals between spikes (see Fig. 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 (synchronisation, Sillito et al. 1994; Kirkland et al. 2000), affecting the spatiotemporal response properties and the amount of information transmitted from dLGN to cortex (McClurkin et al. 1994; Marrokko et al. 1996).

Gradually these observations lead to a more unequivocal interpretation of the action of the corticothalamic feedback in experimental, anaesthetised (!) conditions. The situation, however, is less clear during normal, awake, physiological states without experimental interference. It seems however fair to assume that also “in normal life” the cortex acts mainly facilatory onto the dLGN. In addition, the discussion should not overlook the closed-loop aspect: After all, the corticothalamic influence will within a single loop re-enter the cortex and lead to an altered behaviour also there (Wörgötter

et al. 1998b; Hillenbrand & van Hemmen 2000). The results from chronic inactivation, which certainly more strongly relate 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 rightfully assume that the action of the corticothalamic feedback will be more localised in a physiological situation leading to locally different influences on the dLGN. We would also expect that it is more subtle as compared to the rather coarse effect of experimental cortical inactivation.

As a consequence, in an awake, physiological situation such subtle shifts in corticothalamic activity would most likely 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 will be 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 which enhances the detection of changes in the visual field outside of 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 feature contrast in the dLGN via a centre/surround organisation 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 (see 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, synchronisation processes, which are possibly involved in the encoding of more complex relations between stimuli, heavily rely on tonic activity. Bursts are too short to allow for any synchronisation to take place. It seem likely that also in a physiological state an active corticothalamic feedback shifts the dLGN activity patterns more into tonic states, facilitating such processes.

Taken together, 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 over the last years, functional interpretations, on the other hand, are still to a large degree

speculative. However, due to the detailed physiological understanding, we are now getting in the position of being able to design very detailed biophysical models of retina (as its front end, 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.

		Normal			**Feedback *chronically* inactivated**	
		Syn. EEG	Less-Syn. EEG		Syn. EEG	Less-Syn. EEG
CORTEX	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**	
		Syn. EEG	Less-Syn. EEG		Syn. EEG	Less-Syn. EEG
dLGN	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***

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

Legends

Fig. 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. Small numbers indicate the corresponding stimulus repetition ("sweep"). B) Dot raster diagram of an X-ON-cell response recorded simultaneously to the EEG-trace in (A). The stimulus (flashing bright spot, 1.0 deg., contrast 0.9) timing diagram is depicted on the bottom. The cell responds 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) stimulated also 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)

Fig. 2) Interspike interval histograms (INTHs) from an X-ON-cell stimulated with a flashing bright spot (2.0 deg., contrast 0.9, 100 sweeps, 2s 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. 1998a)

Fig. 3) Peri-stimulus time histograms (PSTHs) from an X-On (A) and a Y-On-cell (B) recorded during different EEG states. Both cells respond rather phasic during synchronized EEG and more tonic during less-synchronized EEG. Stimuli were: A) spot 0.3 deg. contrast 0.9, B) spot 1.0 deg. contrast 0.9 (modified from Wörgötter et al. 1998b).

Fig. 4) Interspike interval histograms (INTHs) from an Y-On cell stimulated with a flashing bright spot (1.0 deg., contrast 0.9, 100 sweeps, 2s 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. 1998a). 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.

Fig. 5) EEG-changes compared to changes in mean impulse rate for dLGN cells recorded at a site which topographically matched the cortical inactivation site ("matching cells") as compared to a control group recorded simultaneously from a non-matching site. The EEG remained unchanged at a ratio of about 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 group of recording on top shows cells without cortical cooling but during a strongly increase in the low-frequency components in the EEG. Both parameters co-vary in these cases. (modified from Wörgötter et al. 1998a)

Fig. 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 deg., contrast 0.9. For further explanation see text. (reproduced with permission from Wörgötter et al. 1998a).

Fig. 7) Cortical inactivation leads to a broadening of the interval peaks in dLGN INTHs. X-ON-cell, stimulus: spot 1.5 deg., 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).

Fig. 8) Receptive field 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 deg x 3-6 deg; contrast $(100\cdot(I-I_0)/(I+I_0))$ 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-center, 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 to 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 receptive fields develops over time. Responses in control hemispheres (a,b) are longer and more pronounced during less-synchronised EEG. The situation is reversed in the experimental hemispheres (c,d), where responses are stronger and have a longer duration during synchronised EEG. (modified from Eyding et al. 2002)

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APPENDIX – 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. 1998a,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 point out some of the more important differences.

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

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 to 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, trans-dural activation of chlorin e_6 with 674nm 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 to 14 days.

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

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-synchronised” (less-syn) and “synchronised” (syn) episodes, using a threshold power ratio of 0.5 (method slightly modified from Li et al. 1999). “Less-synchronised” in the anaesthetised animal is that particular state that most closely resembles a desynchronised EEG in awake animals.

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 inter-spike interval histogram (INTH). Here we will, however only show cross-sections through such intervalograms which correspond to conventional temporally localised 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 receptive field structure.

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.

Cell counting: Complex counting procedures were applied using modified, semi-automatic stereological methods (Guillery & Herrup 1997) to quantify neuronal population density in experimental vs. 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 layer 5A and 5B where a strong drop of cell density exists, which can be used as a distinct feature for accurate alignment.

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. 1998a).

Micro-Iontophoresis: Micro-iontophoresis was performed in the dLGN using multi-barrel pipettes. Depending on the experimental setup, the micro-iontophoresis barrels were filled with gamma-amino butyric acid (GABA, 0.5 M, pH 3.0, saline) or bicuculline methiodide (BICU, 5 mM, pH 3.0, saline).

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 area 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 4x4 micro-pipettes was inserted into the infragranular layers of cortical areas 17 and 18. The lateral distance between two tips was approximately 1000 μm. All pipettes were filled with GABA and attached in parallel in bundles of four to the channels of the Neurophore control unit.

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Corticothalamic Influences on Visual Processing