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Thalamic circuitry and thalamocortical synchrony

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The corticothalamic system has an important role in synchronizing the activities of thalamic and cortical neurons. Numerically, its synapses dominate the inputs to relay cells and to the γ-amino butyric acid (GABA)ergic cells of the reticular nucleus (RTN). The capacity of relay neurons to operate in different voltage-dependent functional modes determines that the inputs from the cortex have the capacity directly to excite the relay cells, or indirectly to inhibit them via the RTN, serving to synchronize high- or low-frequency oscillatory activity respectively in the thalamocorticothalamic network. Differences in the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subunit composition of receptors at synapses formed by branches of the same corticothalamic axon in the RTN and dorsal thalamus are an important element in the capacity of the cortex to synchronize low-frequency oscillations in the network. Interactions of focused corticothalamic axons arising from layer VI cortical cells and diffuse corticothalamic axons arising from layer V cortical cells, with the specifically projecting core relay cells and diffusely projecting matrix cells of the dorsal thalamus, form a substrate for synchronization of widespread populations of cortical and thalamic cells during high-frequency oscillations that underlie discrete conscious events.

Keywords: corticothalamic connections; oscillations; inhibition; excitation; core and matrix

1. INTRODUCTION

In the past two decades, a fundamental circuit diagram of the mammalian thalamus has been established as the result of morphological investigations allied with physiological studies *in vivo* and *in vitro*. It has become clear that the thalamic network is not one that can be viewed in isolation as being solely engaged in the transmission of sensory messages from the periphery to the centres for perception in the cerebral cortex, for thalamic and cortical networks interact in a highly coherent manner during forebrain activities that underlie perception, cognition and the sleep–waking cycle. I shall focus on the centrifugal projection from the cortex to the thalamus and how it interacts with the intrinsic thalamic circuitry to generate synchrony in large-scale assemblies of thalamic and cortical neurons during externally and internally generated brain states.

2. THE CENTRAL POSITION OF THE RETICULAR NUCLEUS IN THALAMIC CIRCUITRY

As is well-known, the GABAergic cells of the thalamic RTN are innervated by collateral branches of thalamocortical and corticothalamic fibres as these traverse a sector of the nucleus defined by its connectivity with the particular dorsal thalamic nucleus and its associated cortical area (Jones 1975). This bi-directional collateral input to the RTN, and the projection of the RTN cells in that sector back to the particular dorsal thalamic nucleus, form the basis of the fundamental circuit diagram of the thalamus common to all mammals. Inputs coming to a nucleus of the dorsal thalamus from the periphery, or from intrinsic brain structures, excite relay neurons, the collaterals of these neurons' cortically projecting axons excite RTN cells which, in projecting back to the same nucleus, form an inhibitory feedback connection to the relay cells. Fibres returning to the thalamus from the cortical area to which the dorsal thalamus projects excite, via their collaterals, cells in the same sector of the RTN, and in this case, the projection of the RTN cells into the dorsal thalamus provides an inhibitory feed-forward to the relay cells. This bi-directional circuitry holds the key to understanding certain aspects of the capacity of the cortex to induce and/or maintain thalamocortical synchrony.

3. CORTICOTHALAMIC TERMINALS PREDOMINATE ON RETICULAR NUCLEUS CELLS

The collateral synapses of corticothalamic axons in the RTN are quantitatively far more numerous than those derived from thalamocortical collaterals or from other sources (Liu & Jones 1999; figure 1). Corticothalamic terminals on cells in the somatosensory sector of the rat RTN account for almost 70% of the synapses that these cells receive, thalamocortical collateral synapses account for some 20–25% and GABAergic synapses *ca.*15–20%. Terminals derived from brainstem and basal forebrain sites in this sector appear to be quite small in number and most do not possess the membrane contacts typical of glutamatergic and GABAergic synapses (Liu & Jones 1991).

As detailed below, all the corticothalamic collateral terminals ending in the RTN are derived from the axons of thalamically projecting neurons with somata located in layer VI of the cortical area related to the particular sector

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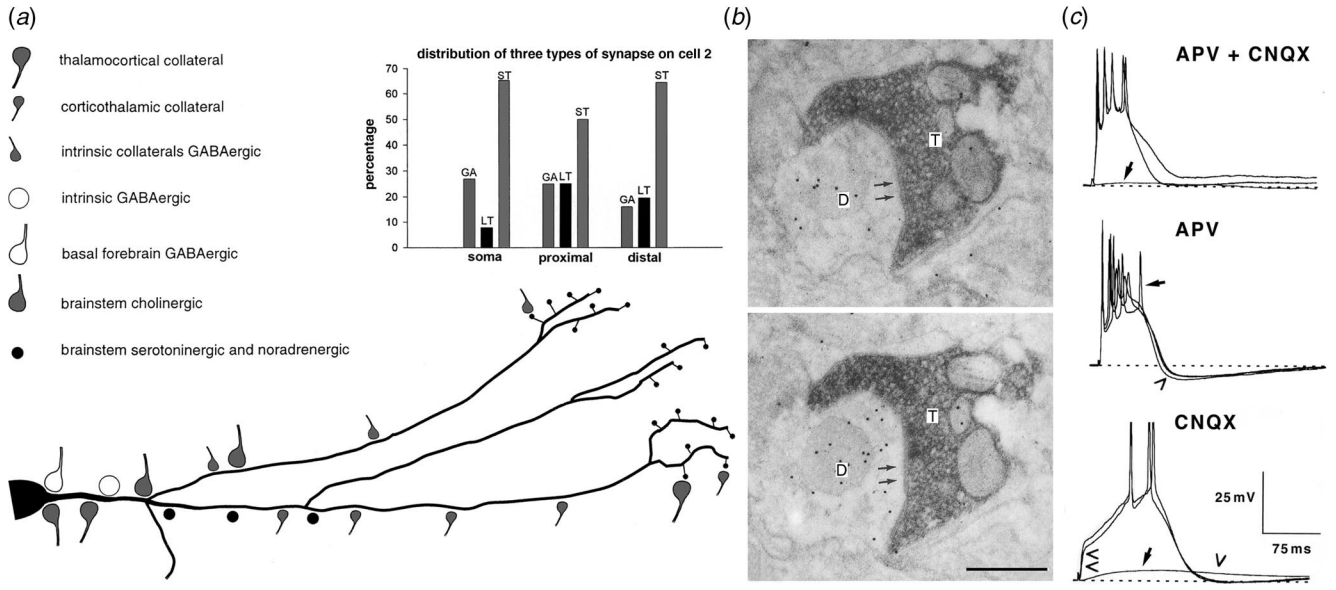

Figure 1. (*a*) Schematic distribution of synapses of various types innervating the reticular nucleus. Inset: quantitative distribution of GABAergic (GA), thalamocortical collateral (LT) and corticothalamic (ST) terminals on soma, proximal and distal dendrites of a labelled cell in the reticular nucleus of a rat. (*b*) Electron micrographs of two sections from a series through a corticothalamic terminal (T) labelled by transported PhAL and synapsing (arrows) on the dendrite of a neuron in the RTN of a rat, labelled for GABA by immunogold particles. Scale bar, 1 μm. (*c*) EPSPs induced in a RTN cell in a mouse thalamocortical slice *in vivo*. Each panel consists of three superimposed traces from whole-cell recordings before, during and after application of NMDA-(APV) and AMPA-(CNQX)-receptor antagonists. Arrow indicates trace recorded during application of the antagonists. The single arrowheads in the middle and lower traces indicate increased after-hyperpolarization (middle panel) and overlap of remaining slow EPSP and after hyperpolarization (lower panel). The double arrowhead in the lower panel indicates early EPSP that is blocked by CNQX. Modified from Jones (2002).

of the RTN. The small terminals of the corticothalamic collaterals have a single small postsynaptic density, which appears to reflect the presence of a single vesicle release site (see below), and are distributed in more or less equal numbers over both proximal and distal dendrites of a RTN cell. When stimulated, corticothalamic fibres induce fast rising EPSPs in RTN cells. These EPSPs have both NMDA and non-NMDA components (Warren & Jones 1997; figure 1). The non-NMDA component is completely AMPA-based, kainate receptors, although present in small numbers, not being activated even by repetitive stimuli (Bolea *et al.* 2001). The less frequent synapses derived from collaterals of thalamocortical fibres are mainly located on the proximal dendrites of the RTN cells and, although in a minority, are distinguished by a larger size and by the presence of large, perforated postsynaptic densities, indicative of multiple vesicle release sites (see below). The GABAergic terminals are, in the main, derived from axon collaterals of the RTN cells (Liu *et al.* 1995*b*), although there is some controversy over the extent to which these collaterals exist (Pinault *et al.* 1997). In some species, dendro-dendritic synapses between distal dendritic protrusions of the RTN cells also form a set of GABAergic synapses (Yen *et al.* 1985).

In some animals, such as rodents, distinct differences in the diameters of corticothalamic and thalamocortical fibres, that provide collateral inputs to the RTN, make it possible to identify the two kinds of collateral synapse physiologically. This may not be possible in certain systems of other animals, such as the visual system of cats in which the diameter range of thalamocortical fibres overlaps that of the corticothalamic fibres (Tsumoto & Tsuda 1981). In all species, a brief electrical stimulus applied to the cerebral cortex or to the underlying white matter elicits EPSCs in RTN cells because of antidromic invasion of thalamocortical collaterals and orthodromic activation of the corticothalamic collaterals. Where the two sets of parent fibres differ in diameter, these EPSCs can be readily distinguished on the basis of latency differences (Golshani *et al.* 2001; Liu *et al.* 2001; figure 2). In the mouse somatosensory sector, there is a latency difference of 2–3 ms.

By using a minimal stimulation paradigm to activate single or small numbers of corticothalamic fibres collateralizing in the somatosensory sector of the rodent RTN *in vitro*, longer latency unitary EPSCs, attributable to collateral corticothalamic synapses, have a consistent amplitude which reflects the presence of a single vesicle release site. However, they have a wide range of rise times, which reflects their distribution over all levels of the dendritic tree (Liu *et al.* 2001; figure 2). By contrast, unitary EPSCs attributable to collateral thalamocortical synapses have large, although variable amplitudes, which reflect the presence of multiple release sites at the synapses. Unlike the corticothalamic EPSCs, they have very consistent rise times, which reflects their proximal location on the dendritic tree. These different characteristics of cortically and thalamically generated EPSCs have special significance in the generation of thalamocortical synchrony (see below).

4. THE CONTRIBUTION OF CORTICOTHALAMIC SYNAPSES TO THE SYNAPTIC GEOGRAPHY OF RELAY NEURONS IN THE DORSAL THALAMUS

Relay cells throughout the dorsal thalamus of all species show a commonality of synaptic organization, and in all

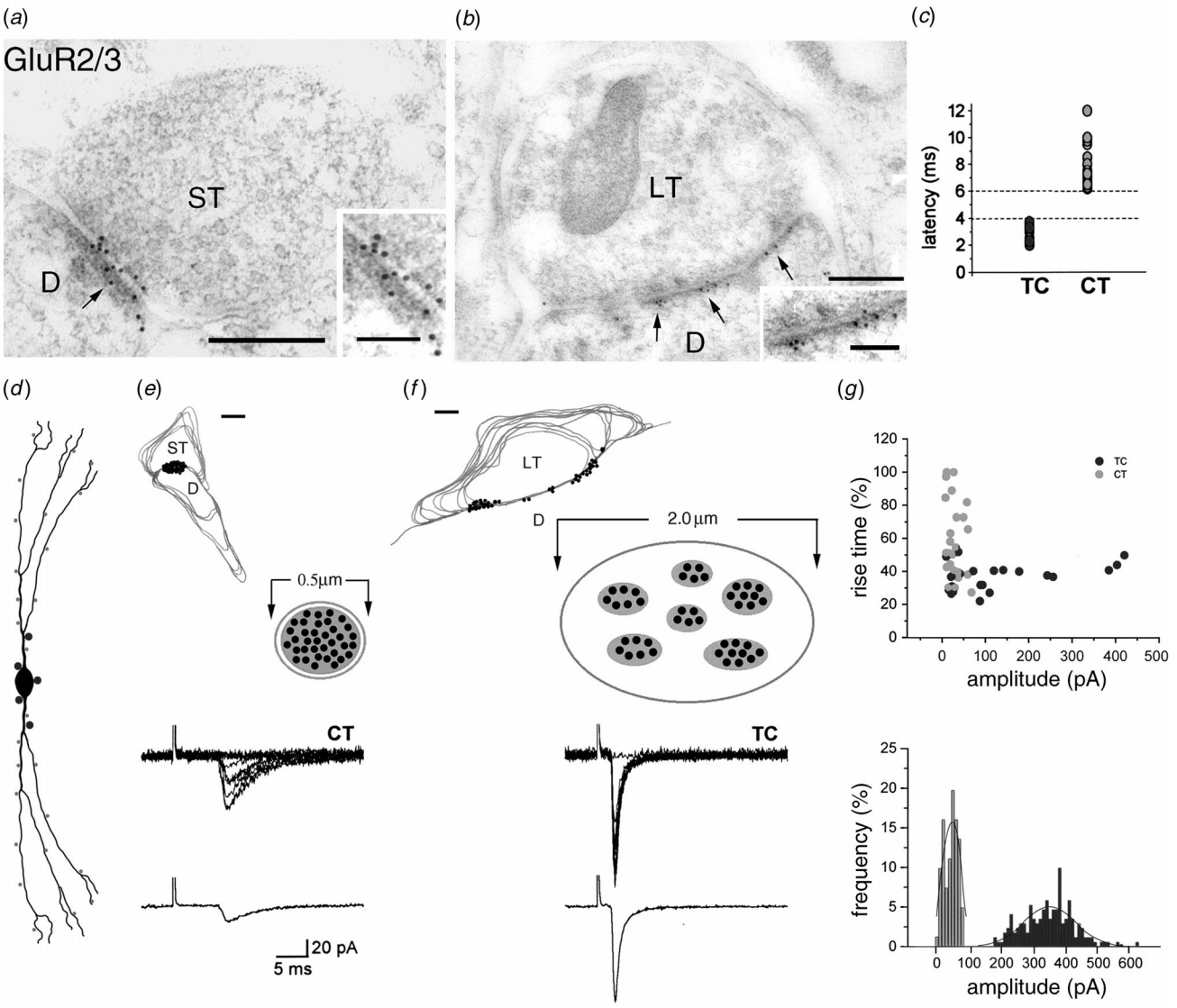

Figure 2. (*a*,*b*) Electron micrographs of terminals of corticothalamic (ST) and thalamocortical (LT) collaterals in the RTN of a mouse. Electron-dense particles represent immunogold labelling for $GluR_2$- and $GluR_3$-receptor subunits at these synapses. Corticothalamic terminals are characterized by a focal synaptic apposition representing a single vesicle release site. Thalamocortical collateral terminals are characterized by multiple appositions representing multiple release sites (arrows). Scale bars, 0.25 and 0.1 μm (insets). (*c*) Bimodal latencies of EPSCs recorded from mouse RTN cells in response to stimulation of subcortical white matter. Shorter latency responses reflect antidromic activation of collaterals of thalamocortical fibres (TC). Longer latency EPSCs represent orthodromic activation of collaterals of corticothalamic fibres (CT). (*d*) Drawing of a RTN cell showing proximal location of thalamocortical collateral synapses and widespread distribution of corticothalamic collateral synapses. (*e*,*f*) Upper: reconstructions from several electron micrographs of corticothalamic (ST) and thalamocortical (LT) collateral synapses terminating on dendrites (D) of RTN cells in mice, with immunogold labelling of postsynaptic densities for $GluR_{2/3}$ subunits. Reconstructed tangential views of each synapse show immunogold particles (dots) located at the single contact of a corticothalamic collateral synapse and multiple release sites at thalamocortical collateral synapse. Lower: 10 successive EPSCs and mean of these EPSCs recorded from RTN cells in response to minimal stimulation of corticothalamic or thalamocortical fibres. (*g*) Collateral thalamocortical EPSCs have larger amplitudes and faster rise and decay times than collateral corticothalamic EPSCs. Upper: relatively constant rise times of minimal thalamocortical EPSCs reflect proximal location of these synapses on mouse RTN cells, but variable amplitudes reflect wider variability in number of release sites at these synapses. Variable rise times of minimal corticothalamic EPSCs reflect the more widespread distribution of these synapses on the cells, but constant amplitudes reflect the single release site. Based on Liu *et al.* (2001).

relay cells, the predominant input numerically is from the cerebral cortex. A few physiologically identified and intracellularly labelled relay cells in the VPN (Liu *et al.* 1995*a*) and in the dorsal lateral geniculate nucleus (Wilson *et al.* 1984) of cats have been examined by serial electron microscopic reconstruction, commonly in association with colabelling of specific synaptic inputs. In these studies, rapidly adapting cells in the VPN, and Y cells in the dorsal lateral geniculate nucleus, were shown to receive *ca.* 5000–8000 synapses over their whole soma-dendritic membrane (figure 3). Approximately 44% of these synapses were derived from corticothalamic fibres and were concentrated on secondary, and particularly on tertiary, dendrites. Approximately 16% were derived from medial lemniscal or optic tract fibres and were concentrated on proximal dendrites, ending with multiple points of synaptic contact,

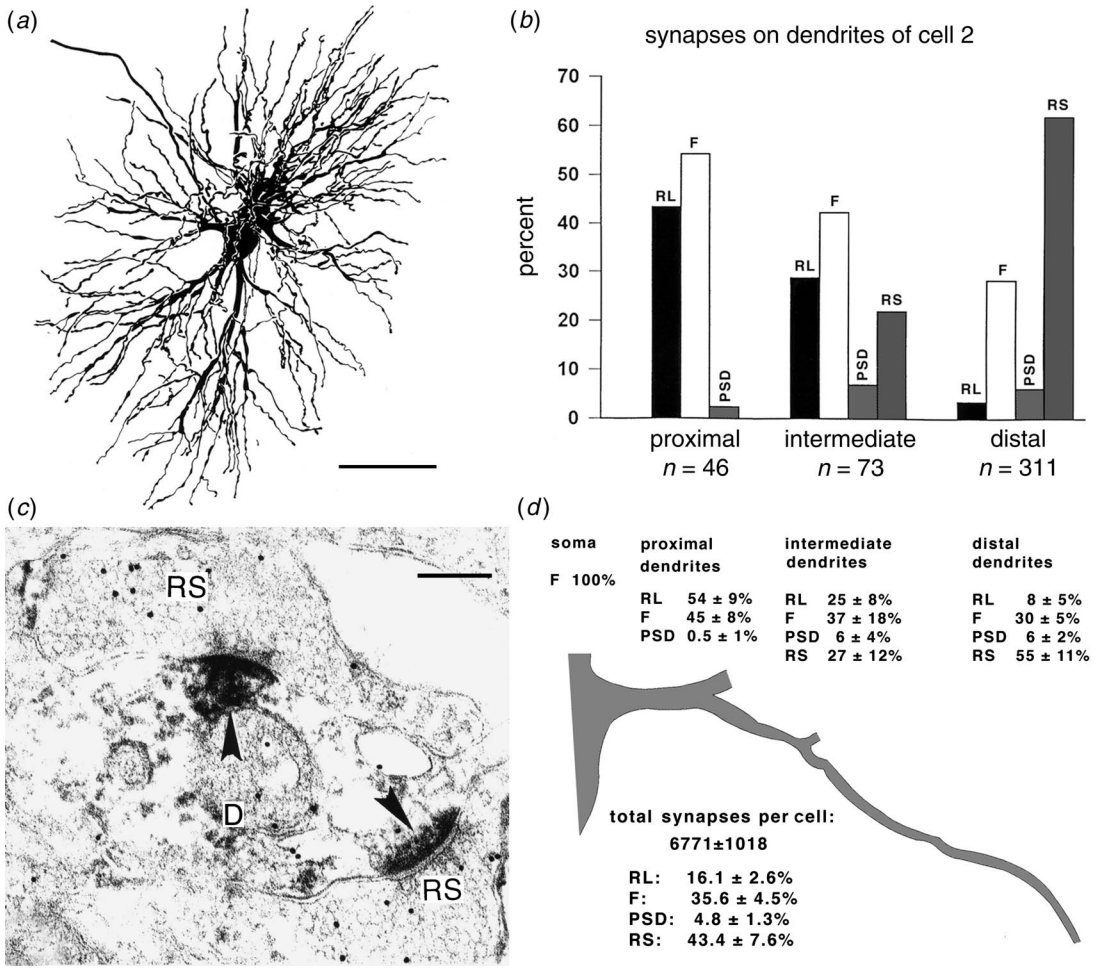

Figure 3. (*a*) Physiologically identified and intracellularly injected relay cell from the VPN of a cat, showing the typical bushy form. Scale bar, 50 μm. (*b*) Distribution of medial lemniscal (RL), GABAergic (F), and corticothalamic (RS) axon terminals, and presynaptic dendrites (PSD) of interneurons on the dendrites of an identified thalamocortical relay cell from the VPN of a cat. (*c*) Electron micrograph of corticothalamic terminals (RS) in a rat, labelled for glutamate by immunogold particles, ending on a dendrite (D) of a relay neuron at synapses in which the postsynaptic density shows strong immunoperoxidase labelling (arrowheads) for alpha-type II calcium/calmodulin-dependent protein kinase. Scale bar, 1 μm. (*d*) Estimated total number of synapses and relative proportions of the major types on a relay cell in the cat VPN. Modified from Jones (2002).

on dendritic protrusions as well as on the shafts of the dendrites. The remaining 40% of synapses were inhibitory (morphologically or by immunostaining for GABA) and tended to be concentrated on proximal and secondary dendrites and on the soma. In the VPN, most of these terminals (36% of the total synapses) were derived from axons of the RTN. A smaller number (5% of the total) were derived from presynaptic dendrites of intrinsic interneurons.

It can be seen from the above that corticothalamic terminals predominate on relay cells, as they do on RTN cells, and it has been calculated that as many as 80% of the axon terminals in a relay nucleus such as the dorsal lateral geniculate nucleus are derived from corticothalamic axons (Van Horn *et al.* 2000). It has sometimes been suggested that nerve terminals arising from non-specific brainstem afferents, particularly the cholinergic group, which are particularly concentrated in the dorsal lateral geniculate nucleus and adjoining sector of the RTN of the cat may, in resembling corticothalamic terminals morphologically, cause the number of corticothalamic terminals to be overestimated (Erisir *et al.* 1997). This does not appear to be a problem of any significance in other thalamic nuclei, where most of these terminals do not end in overt synaptic thickenings and their density is low (Liu & Jones 1991). The dense association of the alpha subunit of type II calcium/calmodulin-dependent protein kinase (CAMKII-α) with the postsynaptic densities of corticothalamic synapses on relay neurons readily permits distinction of these synapses from those derived from non-glutamatergic cells (Liu & Jones 1996; figure 3). This kinase is, however, not expressed in GABA cells, so corticothalamic terminals in the RTN, even when derived from branches of the same axon as those ending in CAMKII-α-positive synapses in an underlying relay nucleus, do not end in association with the kinase (Benson *et al.* 1991, 1992).

5. DUAL EFFECTS OF CORTICOTHALAMIC STIMULATION ON RELAY CELLS

The glutamatergic and therefore excitatory nature of the layer VI-originating corticothalamic input to relay cells is not in doubt and is clearly evident in the NMDA-, AMPA- and metabotropic glutamate receptor-based EPSCs that can be recorded in relay cells under appropri-

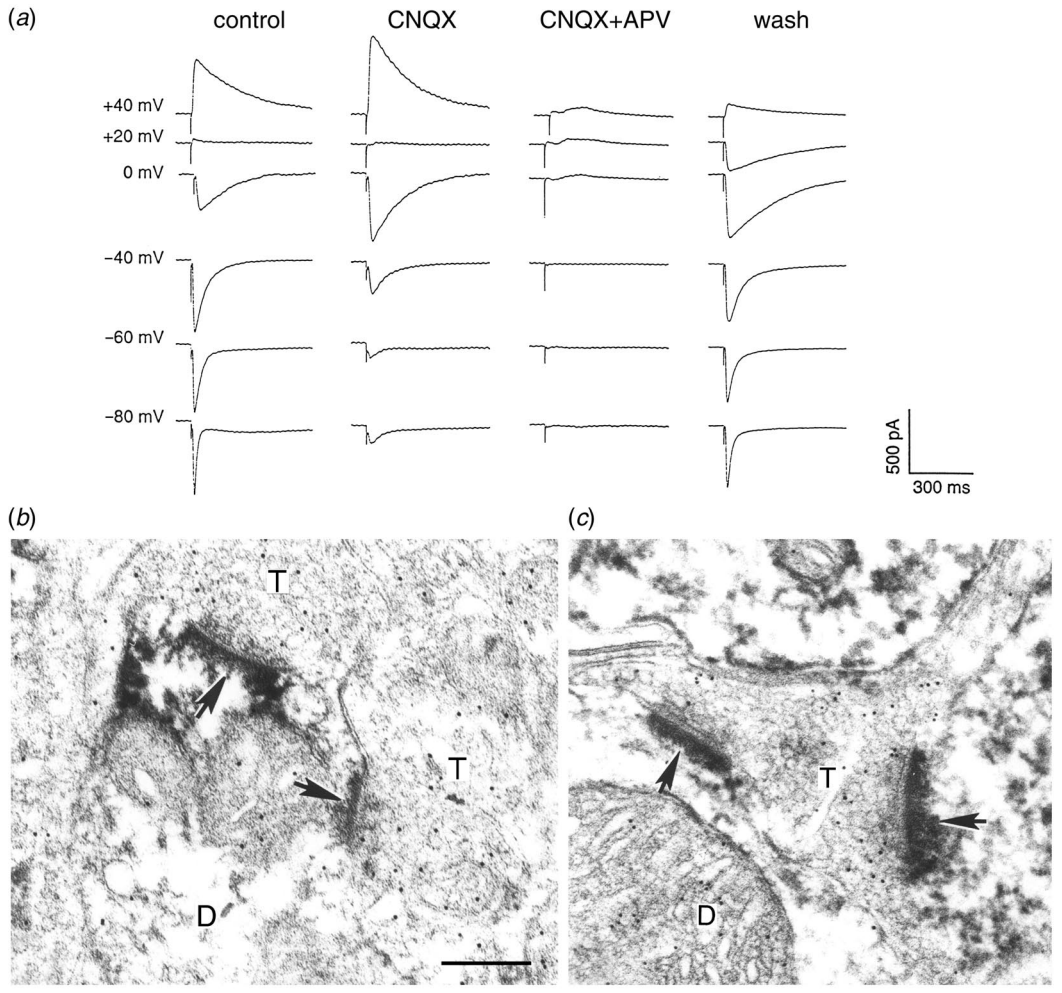

Figure 4. (*a*) Whole-cell recordings from a relay neuron in the VPN of a mouse thalamocortical slice *in vitro*, showing EPSCs recorded at various membrane potentials in response to stimulation of corticothalamic fibres, in the presence of AMPA (CNQX)- and NMDA (APV)-receptor antagonists. (*b*,*c*) Electron micrographs of corticothalamic axon terminals (T) labelled by immunogold particles for glutamate immunoreactivity, ending on dendrites at synapses in which the postsynaptic densities (arrows) are labelled by immunoperoxidase for NMDA (*a*) or AMPA (*b*) receptors. D, dendrites. Rat. Scale bar, 0.5 μm. Modified from Jones (2002).

ate conditions (figures 4 and 5; McCormick & von Krosigk 1992; Kao & Coulter 1997; Turner & Salt 1998; Golshani *et al*. 1998; von Krosigk *et al.* 1999). However, the presence of the collateral input from the same corticothalamic fibres to the GABAergic cells of the RTN also makes it possible for the cortex to exert a most profound disynaptic, inhibitory effect on relay cells, and, according to some, under normal conditions in the intact brain, inhibition may be the predominant effect of the cortex over the thalamus (Steriade 2001). It would appear, however, that corticothalamic stimulation can generate either inhibitory or excitatory responses in relay cells depending, to a large extent, upon the functional state of these cells, a state dependent, in turn, on their possession of a remarkable set of voltage-dependent membrane conductances.

When thalamic relay cells are relatively hyperpolarized, as occurs naturally during sleep and drowsy inattentiveness, or under experimental conditions, the disynaptic inhibition mediated by the RTN is commonly sufficient to overcome a weak direct excitatory effect of corticothalamic stimulation. *In vitro*, with relay cells held at a membrane potential negative to −55 mV, a single weak electrical pulse applied to corticothalamic fibres will lead to a small, short latency EPSP in a relay cell, but this tends to be cut down by a deep and prolonged IPSP lasting up to 100 ms and representing the disynaptic input from the RTN (figure 6). This IPSP consists of both $GABA_A$ and $GABA_B$-receptor-mediated components consistent with the presence of both $GABA_A$- and $GABA_B$-receptors at the reticulothalamic synapses. These synapses are heavily concentrated on relay cells and tend to avoid intrinsic interneurons (Liu *et al.* 1995*b*; Wang *et al.* 2001). Hyperpolarized thalamic relay cells are predisposed to discharge action potentials in burst firing mode and, as the cells recover from the RTN-mediated inhibition, the low threshold calcium current (I_T) is deinactivated and the cells fire a burst of action potentials. This burst excites, via the collaterals of thalamocortical fibres, the RTN cells. Re-excitation of the RTN cell is led by a stepwise EPSP, in which each step increment in amplitude can be correlated with one of the action potentials of the burst in a connected relay cell. The burst of action potentials in the RTN cells serve to re-inhibit the relay cells, which burst again on recovering from the new IPSPs, and the cycle continues as a low-frequency oscillation at 7–14 Hz, the spindle frequency. Each successive event in the oscillation

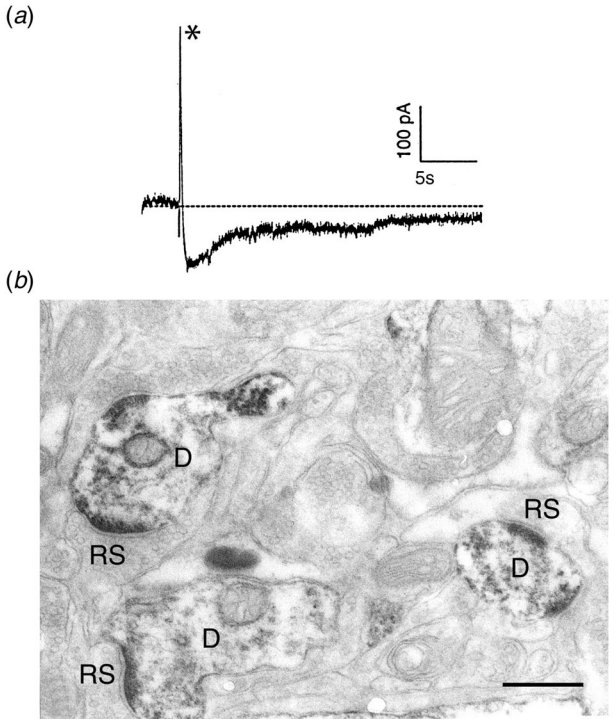

Figure 5. (*a*) Long-lasting EPSC in a relay cell in response to stimulation of mouse corticothalamic fibres in the presence of NMDA, AMPA- and $GABA_A$-receptor antagonists, and mediated by metabotropic glutamate receptors. Asterisk indicates preceding $GABA_B$-mediated IPSC. (*b*) Corticothalamic terminals (RS) in the VPN of a rat ending on dendrites (D) that are strongly immunoreactive for metabotropic glutamate receptor $mGluR_{1a}$. Scale bar, 0.5 μm. Modified from Jones (2002).

of the relay cell is a facsimile of its predecessor: inhibition succeeded by burst firing (von Krosigk *et al.* 1993; Warren *et al.* 1994; Bal *et al.* 1995; Blumenfeld & McCormick 2000). The effect of the cortex under these experimental conditions is to generate a spindle oscillation that tends to travel across the thalamus, as more and more RTN cells and relay cells are recruited by the divergence and overlap of the collateral connectivity joining the dorsal thalamus and the RTN (Kim *et al.* 1995). *In vivo*, the cortex may be more involved with synchronizing low-frequency oscillations that commence in the thalamus and occur more or less simultaneously throughout that structure (Contreras *et al.* 1996; Contreras & Steriade 1997). Although the corticothalamic system is particularly powerful in inducing spindle oscillations, it is the RTN that is the prime mover in synchronizing the oscillations of cells throughout the thalamocorticothalamic network. Its capacity for synchronization of low-frequency oscillations in relay cells is enhanced when the weak inhibitory effects of one RTN cell on another are removed (Huntsman *et al.* 1999; Sohal *et al.* 2000).

For the corticothalamic projection to induce low frequency oscillations in the thalamic network via the disynaptic inhibitory effect of the RTN, this disynaptic inhibition has to be sufficiently powerful to overcome the direct, monosynaptic excitation of relay cells by the corticothalamic fibres. Modelling studies, in which the inputs to RTN cells and relay cells are set at equal strengths, result in a failure to elicit oscillatory activity in the network (Destexhe *et al.* 1998). Recent observations show that although made by branches of the same axon, the synapses of corticothalamic fibres on RTN cells are indeed more powerful than those on relay cells (Golshani *et al.* 2001).

Unitary EPSCs can be recorded in rodent relay cells and RTN cells *in vitro* in response to the stimulation of a small number of corticothalamic fibres and under low Ca^{2+} conditions, in which the probability of vesicle release at the corticothalamic synapses is reduced to close to zero (figure 7). The unitary corticothalamic EPSCs in the RTN cells recorded under these conditions (and with GABA- and NMDA-receptor based responses excluded) are nearly three times larger than in relay cells (Golshani *et al.* 2001). This AMPA-receptor-based difference in synaptic strength depends upon marked differences in the composition of AMPA-receptors at the two synapses. High resolution, quantitative immunoelectron microscopy in rodents reveals that there are nearly three times as many $GluR_4$ receptor subunits at corticothalamic synapses on RTN cells than at corticothalamic synapses on relay cells (figure 7). $GluR_3$ subunits are present in equal numbers at these synapses and $GluR_1$ and $GluR_2$ subunits are not expressed in the rodent thalamus (Liu *et al.* 2001). Comparing the enrichment of $GluR_4$ receptor subunits at the corticothalamic synapses on RTN cells with those on relay cells, channel opening times should be longer in RTN cells and account for the larger corticothalamic EPSCs in these cells. $GluR_4$ receptor subunits are not enriched at collateral thalamocortical synapses at which they appear in equal proportions with $GluR_3$ subunits (figure 7). At the larger collateral thalamocortical synapses, however, the overall number of AMPA-receptor subunits is much higher than at the corticothalamic synapses. This may provide the capacity for the powerful re-entrant excitation of the RTN cells by bursts of action potentials in relay cells during the course of spindle oscillations. Some of the variance in the rise times of the unitary EPSCs, engendered in RTN cells by the thalamocortical collaterals, may be attributable to the variable number of subunits located at each of the segments of the perforated synapse.

Under conditions in which both RTN cells and relay cells are relatively depolarized, corticothalamic stimulation results in strong excitation of the cells and can lead to high frequency oscillations in the thalamocorticothalamic network. Under these circumstances, relay cells tend to discharge trains of action potentials at 20–80 Hz (Steriade *et al.* 1998). At membrane potentials positive to −45 mV, thalamic neurons *in vitro* display spontaneous 20–80 Hz oscillations of membrane potential that are dependent on activation of high threshold Ca^{2+} channels located in dendrites (Pedroarena & Llinás 1997; Toth & Crunelli 1997). These oscillations are usually sub-threshold for spike generation but protracted depolarization, under the influence of volleys of corticothalamic stimuli above 10 Hz, leads to intermittent high-frequency clusters of spikes (Pedroarena & Llinás 2001). As stimulation frequency increases above 10 Hz, EPSP enhancement leads to repetitive firing, and the number of spikes evoked by successive EPSPs progressively increases, probably as the result of short-term presynaptic facilitation, frequency-dependent activation of NMDA-receptors and amplification of the EPSPs by the release of high threshold calcium conductances located in distal dendrites

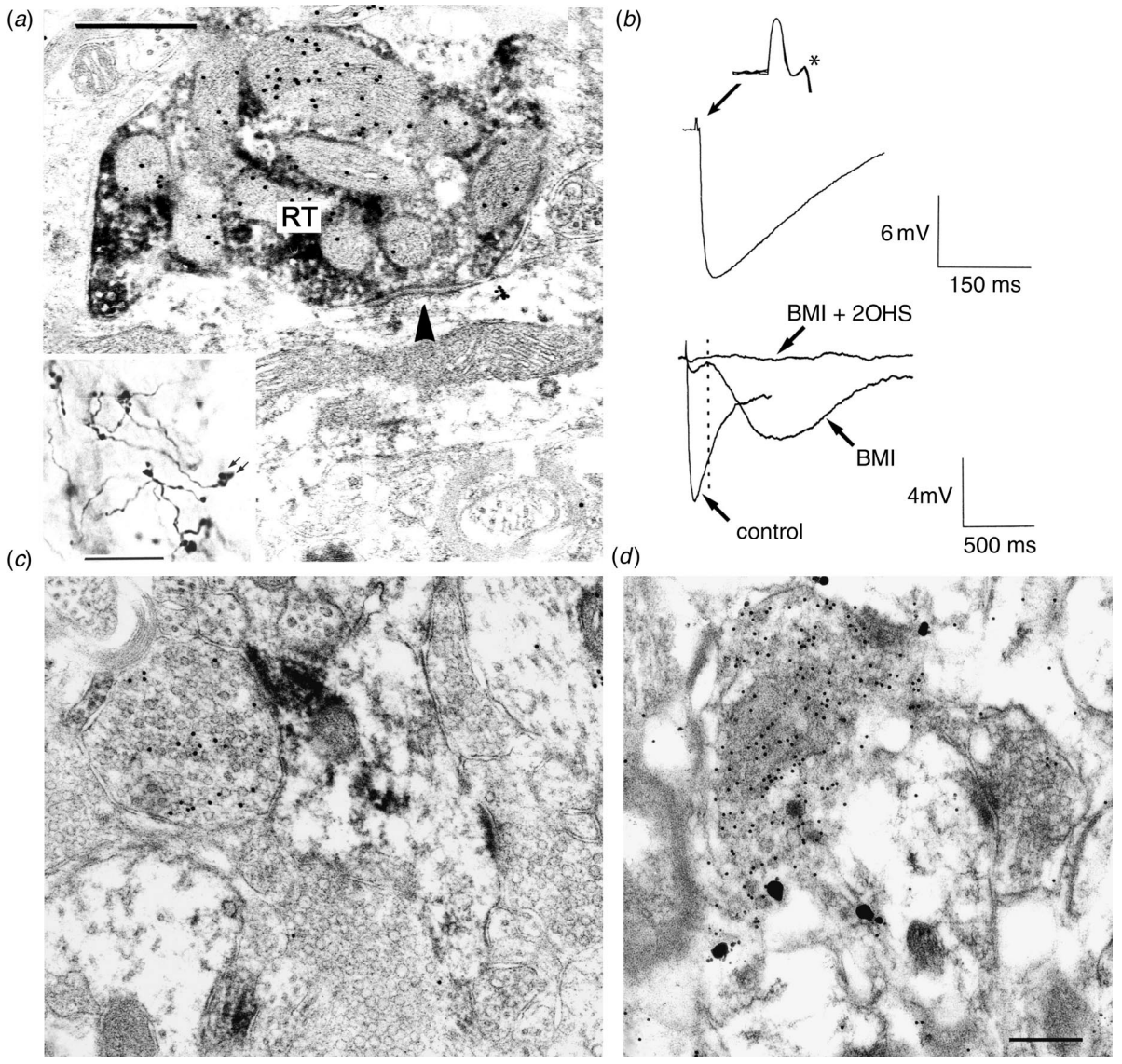

Figure 6. (*a*) Electron micrograph showing a terminal (RT) of a RTN axon labelled by peroxidase for transported PhAL and by immunogold particles for GABA, ending (arrowhead) on the dendrite of a relay cell in the VPN of a cat. Scale bar, 1 μm. Inset: light micrograph of labelled terminal branches of the axon. Scale bar, 10 μm. From Liu *et al.* (1995*a*). (*b*) Whole-cell recording from a relay neuron in the VPN of a mouse thalamocortical slice *in vitro*. In upper panel a single weak electrical stimulus (arrow) applied to the corticothalamic fibres elicits a small monosynaptic EPSP (asterisk in enlarged inset) followed by a deep and long-lasting disynaptic IPSP resulting from collateral corticothalamic excitation of the RTN. In the lower panel, this IPSP is shown to consist of $GABA_A$ and $GABA_B$ components by application of selective antagonists bicuculline (BMI) and 2-hydroxysaclofen (2OHS). (*c*,*d*) Electron micrographs showing putative RTN terminals in the VPN of a rat labelled by small immunogold particles for GABA. (Scale bar in (*d*) also applies to (*c*).) Terminal in (*c*) ends in association with a synaptic contact labelled by immunoperoxidase for $GABA_A$-receptors. In (*d*) $GABA_B$-receptors, labelled by large immunogold particles are not associated with synaptic membranes. Scale bars, 1 μm. Modified from Jones (2002).

(Pedroarena & Llinás 1997, 2001). Under relatively depolarized conditions, therefore, as in attentive wakefulness *in vivo*, relay cells tend to be entrained by high-frequency corticothalamic stimuli. Because high frequency stimulation of corticothalamic fibres is also effective in activating metabotropic glutamate receptors resulting in protracted slow EPSPs (McCormick & von Krosigk 1992; Golshani *et al.* 1998), persistent depolarization of the relay cells would be promoted. The high frequency coherent activity of thalamic nuclei, and the cortical areas to which they project resulting from the interactions between cortex and thalamus, could be a key substrate of forebrain activities underlying perception and cognition.

6. TWO CLASSES OF CORTICOTHALAMIC FIBRE WITH DIFFERENT THALAMIC TERMINATIONS

It is now well known that the cerebral cortex provides two kinds of feedback to the thalamus, via the projections of two distinct classes of pyramidal cell with somata located in different layers. Most cells projecting to a particular thalamic nucleus have somata located in layer VI of the cortical area related to that nucleus. A smaller, but consistent, number is almost invariably found in layer V of the same area and seem to interact primarily with different thalamic nuclei (reviewed in Steriade *et al.* 1997). The layer VI and layer V corticothalamic cells have very differ-

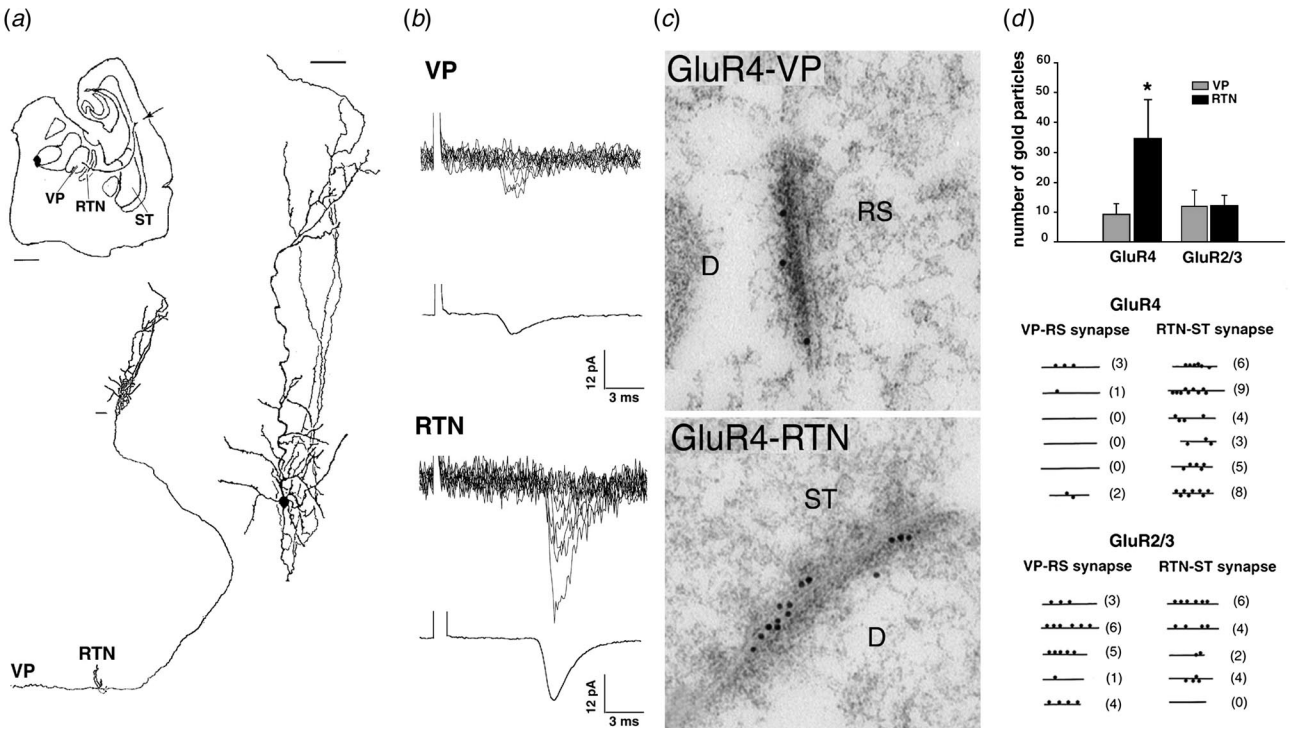

Figure 7. (*a*) Camera lucida drawings showing location and morphology of a typical layer VI corticothalamic cell from a mouse thalamocortical slice preparation (upper left). The axon branches to innervate both the RTN and continue into the VPN. Two sets of 10 superimposed traces and their means, showing EPSCs recorded from a ventral posterior cell and from a RTN cell in response to minimal stimulation of corticothalamic fibres. Amplitudes of minimal EPSCs in RTN cells are approximately three times larger than those in VPN cells. Immunogold particles represent labelling for $GluR_4$-receptor subunits at mouse corticothalamic (RS) synapses in VPN and RTN and show that there are more $GluR_4$-receptors at these synapses in the RTN. The number of immunogold particles representing $GluR_4$ and $GluR_{2/3}$-receptor subunits at four serially sectioned corticothalamic synapses in VPN and RTN. The number of $GluR_4$-related particles at corticothalamic synapses on RTN cells is approximately three times greater than at corticothalamic synapses on VPN cells. The number of particles representing $GluR_{2/3}$-receptor subunits is approximately equal at corticothalamic synapses in VPN and RTN. From Golshani *et al.* (2001).

ent intracortical morphologies and their axons have different patterns of ramification and termination in the thalamus.

Corticothalamic neurons of layer VI are typically small, pyramidal cells with a narrow, vertical dendritic field, centred on a short apical dendrite, that ends by branching in the middle layers of the cortex among the terminations of thalamocortical fibres (figure 8). Here, the cells receive monosynaptic inputs from the thalamocortical fibres. The axon of a layer VI corticothalamic cell, before leaving the cortex, gives off two or three recurrent collaterals which typically ascend within the confines of or closely adjacent to the vertical dendritic field of the cell (Ojima *et al.* 1992; Ojima 1994; figure 8). Each cell, therefore, influences a relatively narrow zone of the cortical area in which it lies. The axon of the cell projects only to the thalamus. As it enters the thalamus, it gives off one or two short collaterals in the RTN and then terminates in a relatively narrow zone, in appropriate topographic order, only in the dorsal thalamic nucleus from which its parent cortical area receives input. Some deep layer VI cells in rodents can have terminations extending across two related nuclei such as the ventral posterior and medial nucleus of the posterior group (Hoogland *et al.* 1987; Bourassa *et al.* 1995). Although ending in a relatively restricted zone of the related thalamic nucleus, the terminals of a single layer VI corticothalamic cell can apparently influence thalamic relay cells that project to regions of cortex outside the narrow cortical zone in which it resides. Corticothalamic axons terminating in the A laminae of the dorsal lateral geniculate nucleus of the cat, for example, concentrate their terminals in a 500 μm wide zone but some terminals extend for up to 1500 μm beyond that (Murphy & Sillito 1996). In other words, the corticothalamic axon can influence an extent of the visual field representation in the lateral geniculate nucleus many times greater than that represented in the cortical column in which its parent cell resides. In rodents, too, fibres derived from a cell beneath a single cortical barrel in the somatosensory cortex may extend terminals into VP barreloids adjacent to the barreloid that provides input to that cortical barrel, and thus into thalamic regions representing other facial vibrissae (Hoogland *et al.* 1987; Bourassa *et al.* 1995).

Corticothalamic cells whose somata lie in layer V are quite different from those of layer VI and are characterized by extensive axonal ramifications in cortex and thalamus. The layer V cells are typically pyramidal in form, with relatively large somata, and have a stout apical dendrite ascending to layer I of the cortex and ending there in a tuft of branches. The axon is thick and gives off several horizontal collaterals that extend for a considerable distance through layers III and V of the cortex (figure 8). The thalamus is only one of the projection targets of the axon for, depending on the area in which the parent cell

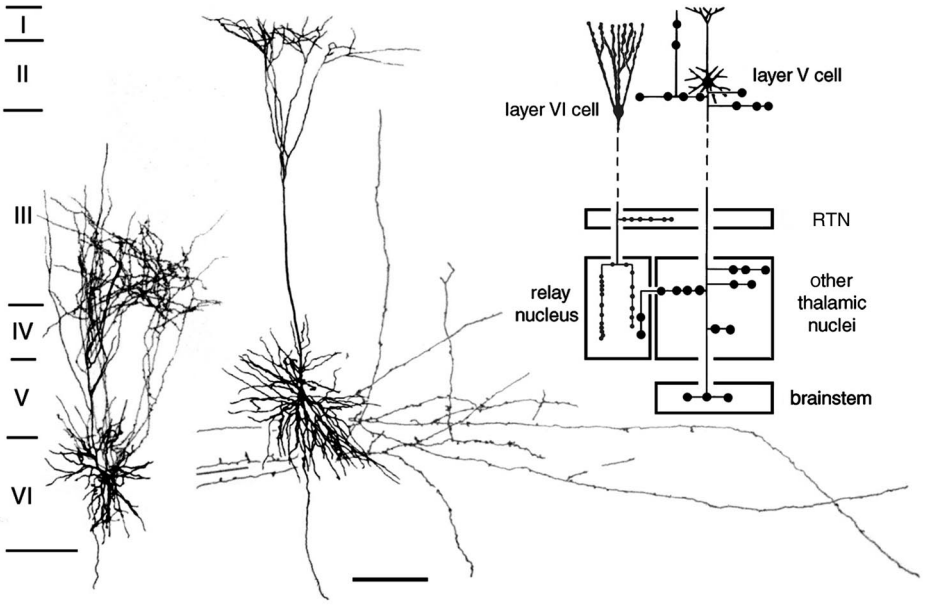

Figure 8. Left: camera lucid drawings of corticothalamic cells in the auditory cortex of the cat, intracellularly labelled with horseradish peroxidase or biocytin. Corticothalamic cells in layer VI have a vertical organization of intracortical axon collaterals while corticothalamic cells in layer V have a horizontal distribution of intracortical collaterals. Right: terminal distribution of axons of layer VI and layer V corticothalamic cells in the cat thalamus, showing focused nature of layer VI projection, with collaterals in the RTN, and distributed nature of layer V projection without collaterals in the RTN. Based on Ojima *et al.* (1992) and Ojima (1994).

lies, the axon, after giving branches to the thalamus, will continue on to the tectum, to other parts of the brainstem or to the spinal cord. Unlike the axon of a layer VI corticothalamic cell, the axon of the layer V cell does not give off collaterals to the RTN and, within the dorsal thalamus, its terminations are not restricted to the nucleus from which its parent cortical area receives inputs. Instead, terminations extend into one or more adjacent nuclei, although in each nucleus the terminals can be more highly focused than those of layer VI cell axons. In the case of cells with somata located in the motor and somatosensory areas of the cortex, these additional nuclei commonly include those of the intralaminar system. In cells in the primary visual cortex, nuclei of the pulvinar–lateral posterior complex are the targets, and in cells in the primary auditory area of the cortex, the dorsal and magnocellular nuclei of the medial geniculate complex are the targets (figure 8). In the dorsal thalamus, the axons of the layer V corticothalamic cells terminate in small numbers of large boutons, quite unlike the numerous small boutons of layer VI corticothalamic cells. These larger boutons often enter into synaptic relationships with relay cells that resemble those of ascending afferent fibres, rather than those of the terminals of the layer VI cells. Below, we shall see that the layer V originating axons may preferentially engage a particular type of thalamocortical relay cell.

7. INTERACTIONS BETWEEN CORTEX AND THALAMUS DURING HIGH FREQUENCY OSCILLATORY ACTIVITY

High frequency oscillations of large populations of cortical and thalamic neurons in the γ-range (20–50 Hz) are often thought to be concomitants of forebrain activities that underlie perception, cognition and directed attention (Llinás & Paré 1991, 1997; Singer & Gray 1995). In the sensory systems of the cerebral cortex, large-scale synchrony of neurons in the areas that form links in the chain of corticocortical processing, and in their thalamic nuclei, may be necessary to ensure the binding of separate elements of sensory experience into a single cognitive event. The focused, topographically ordered projections of thalamic relay neurons as traditionally understood, do not seem appropriate for dispersing thalamic activity across multiple cortical areas that this idea demands. In searching for diffuse thalamocortical connections that might serve this purpose, attention has tended to be directed to the intralaminar nuclei of the thalamus and to their putatively widespread projections to layer I of the cortex. However, we now know that the intralaminar nuclei each project to relatively restricted regions of the cerebral cortex, that their axons are not excessively widely distributed, and some appear to end in deeper layers rather than in layer I (reviewed in Steriade *et al.* 1997). Moreover, many intralaminar cells project to the striatum rather than to the cortex. Recent studies on relay cells, identified in monkeys by specific cytological markers, have revealed a population of cells with the dispersed cortical projections appropriate for expanding thalamocortical activity across the cortex, and in their relationships to the layer V corticothalamic projection could form a substrate for entraining large constellations of thalamic and cortical neurons in synchronous activity that underlies discrete cognitive events (Jones 1998, 2001).

8. THE CORE AND MATRIX OF THE PRIMATE THALAMUS

Immunocytochemical staining for two calcium-binding proteins, parvalbumin and 28 kDa calbindin, has revealed

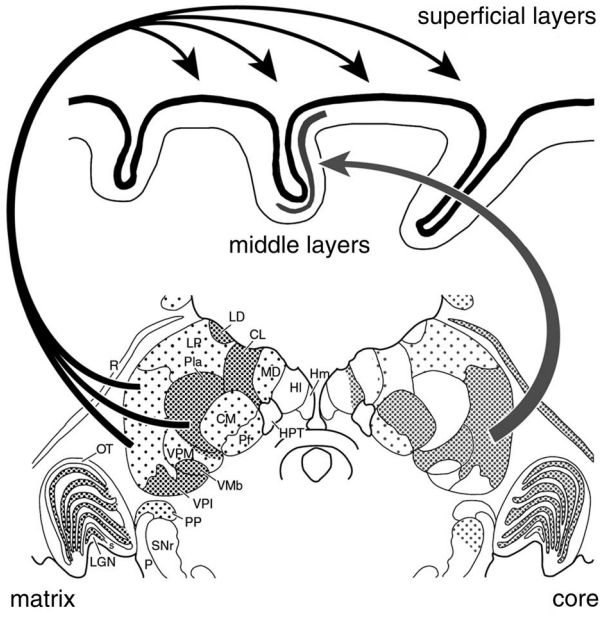

Figure 9. The lower part of figure shows a frontal section through the middle of a macaque monkey thalamus on which the relative distributions and concentrations of calbindin matrix cells (left) and parvalbumin core cells (right) are plotted. Density of dots represents relative density of each cell type. The upper part of figure shows schematically the projection of the matrix to superficial layers of the cerebral cortex over a relatively wide extent. Core cells restricted to individual nuclei, here exemplified by the VPN, project in a topographically ordered manner to middle layers of single cortical fields. From Jones (2001). Abbreviations refer to thalamic nuclei. For further details, see Jones (2001).

two distinct classes of relay neurons in the thalamus of monkeys and certain other primates (see Jones & Hendry 1989; Diamond *et al*. 1993; figure 9). Calbindin immunoreactive neurons are distributed widely throughout the dorsal thalamus and can be found in each of its nuclei. They are slightly smaller than parvalbumin cells but much larger than the intrinsic GABAergic neurons (Rausell *et al.* 1992) and tend to be diffusely dispersed throughout the nuclei. Parvalbumin immunoreactive neurons are found only in the principal sensory and motor relay nuclei, in certain nuclei of the pulvinar and in some intralaminar nuclei. In these nuclei, they typically form large, dense clusters associated with densely terminating afferent fibres, which are themselves parvalbumin immunoreactive. The parvalbumin cells form a core imposed on a diffuse background matrix of calbindin cells.

There is a superficial impression of complementarity in the distributions of calbindin and parvalbumin cells and, where parvalbumin cells are absent, calbindin cells are usually found in increased numbers. In the dorsal lateral geniculate nucleus, parvalbumin cells are located only in the magno- and parvocellular layers, while calbindin cells are concentrated in the S-layers and interlaminar plexuses between the principal layers (Jones & Hendry 1989; Hendry & Calkins 1998; figure 10). However, the calbindin cells spread throughout the nucleus and are continuous with a larger population of calbindin cells in the adjoining inferior pulvinar nucleus (Jones 1998). In VPN, zones of calbindin cells are intercalated among large masses of parvalbumin cells that form the core of the nucleus, and are concentrated in a parvalbumin deficient (s) zone along the posteromedial aspect of the ventral posterior medial nucleus (figures 9 and 10), where they are continuous with a large population of calbindin cells that fill the posterior and anterior pulvinar nuclei. The ventral medial geniculate nucleus is dominated by parvalbumin cells and has only a few calbindin cells (figure 10). The dorsal nuclei have a mixed population of calbindin and parvalbumin cells, with calbindin cells increasing posteriorly where they are continuous with those of the inferior pulvinar nucleus. The magnocellular nucleus possesses islands of calbindin cells alternating with islands of parvalbumin cells. In all dorsal thalamic nuclei where parvalbumin cells are concentrated, histochemical staining for metabolic enzymes such as cytochrome oxidase is high, while in calbindin-rich zones cytochrome oxidase staining is weak.

In their projections upon the cerebral cortex, parvalbumin cells are well-organized topographically so that adjacent groups of cells project to adjacent regions of a single cytoarchitectonic area of the cortex in which they terminate in localized (*ca*. 600 μm) zones of terminals in the middle layers (deep layer III and layer IV) (figure 9). Calbindin cells have more diffuse projections, and adjacent cells in a nucleus can project to two different (although usually adjacent) cortical areas (Rausell and Jones 1991*a*,*b*; Rausell *et al.*1992). In the cortex, their axons terminate in superficial layers (layers I, II and upper III). Where a thalamic nucleus contains both parvalbumin and calbindin cells, therefore, it has both focused, area-specific, middle-layer projections from parvalbumin core cells, and diffuse, superficial-layer projections from calbindin matrix cells (figure 9). A dual projection of this type is not confined to one particular type of dorsal thalamic nucleus for it can be found in both relay nuclei and intralaminar nuclei. In nuclei in which only calbindin cells are found, diffuse, superficial layer projections are the norm (figure 9). These can also be found in nuclei that have been traditionally classified as relay, or intralaminar, and may have a special significance, as outlined below.

The focused and diffuse nature of the cortical projections of core and matrix cells is a reflection of their inputs from subcortical pathways. Dorsal thalamic nuclei with a high density of parvalbumin core cells, for example, the ventral posterior, the laminar dorsal lateral geniculate and the ventral medial geniculate nuclei, receive the terminations of afferent pathways that are highly organized topographically and in which neurons have highly localized receptive fields and specific stimulus–response properties. The fibres of these pathways, i.e. the medial lemniscus, the P and M components of the optic tract, and the brachium of the inferior colliculus are parvalbumin immunoreactive and terminate with a high degree of topographic order among the parvalbumin core cells.

Nuclei, and portions of nuclei, that have a high density of calbindin matrix cells, in contrast, receive the terminations of ascending pathways such as the spinothalamic tract and brainstem tegmental auditory pathways that tend to be more diffusely organized, and less directly connected to the peripheral receptors. Their fibre terminations spread diffusely through large regions of the thalamus and are unrestricted by borders between nuclei (figure 9), although there are some fibres that can be regarded as

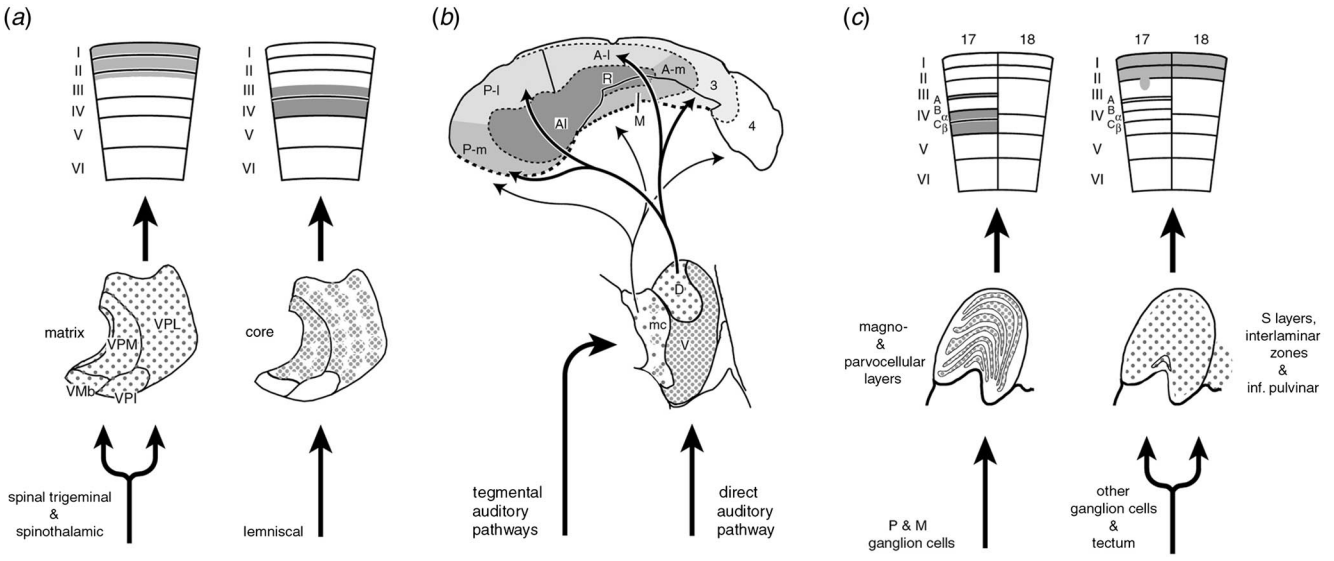

Figure 10. Schematic views of the diffuse and specific subcortical inputs that terminate in the matrix and core compartments of the VP (*a*), medial geniculate (*b*) and dorsal lateral geniculate (*c*) nuclei of macaque monkeys, and the layer-specific and diffuse or focused projections of these compartments to the cerebral cortex. In (*a*) and (*c*), cortical areas are indicated by schematic vertical sections with the layers indicated; in (*b*) the surface of the supratemporal plane, with the different auditory fields delineated, is shown. Based on Jones (2001).

quite specific in the spinothalamic tract and in the inputs to the S-layers and interlaminar plexuses of the dorsal lateral geniculate nucleus. Neurons in the dorsal nuclei of the medial geniculate complex, which have a large density of calbindin cells, receive inputs from the less direct auditory pathways, for example, are not tonotopically organized, fatigue easily and usually require novel stimuli for activation. The spinothalamic tract, whose patch-like terminations are distributed in calbindin-rich zones in and around the VPN (Rausell *et al.* 1992) is dominated by fibres with large receptive fields and multi-modal inputs. Fibres ascending from the deeper layers of the superior colliculus, and terminating in large numbers in the calbindin-rich inferior pulvinar nucleus, spill over into the dorsal lateral geniculate to terminate among the calbindin cells of the S-layers and interlaminar plexuses. These matrix regions are innervated by the least well-characterized population of retinal ganglion cells that includes blue-on cells (Martin *et al.* 1997).

9. INVOLVEMENT OF CORE AND MATRIX CELLS AND CORTICOTHALAMIC PROJECTIONS IN WIDESPREAD SYNCHRONY OF THE THALAMUS AND CEREBRAL CORTEX

The relay cells of the thalamic core, with their focused projections to an individual cortical area, clearly form the basis for the relay of place- and modality-specific information to the cortex whereas those of the thalamic matrix form a more obvious basis for the dispersion of activity in the thalamocortical network across larger areas of cortex. Within a zone of cortex, the terminations of matrix cell axons on distal dendrites in superficial layers and of matrix cell axons on more proximal dendrites in middle layers should serve as a coincidence detection circuit, providing for a high degree of temporal integration between inputs coming from the two classes of thalamic cells (Llinás & Paré 1997; figure 11). Coincidence of this kind should promote synchronous activity in the cells of individual cortical columns and in any group of columns activated by the same stimulus. Activity in these columns would then be returned via layer VI corticothalamic cells to the thalamic nucleus from which they receive input, serving to reinforce thalamocortical synchrony. This activity would be spread to other cortical columns in the same cortical area and in adjacent cortical areas via the diffuse projections of matrix cells in the thalamic nucleus through which externally or internally generated activity was first passed to the cortex. However, other thalamic nuclei would be recruited via the diffuse corticothalamic projections of layer V corticothalamic neurons and, through the projections of matrix cells in these nuclei, other cortical areas would become involved. It is not without significance that the principal targets of layer V corticothalamic axons appear to be nuclei that are rich in matrix cells (e.g. the anterior pulvinar nucleus for layer V cells of the somatosensory cortex, certain other pulvinar nuclei for the visual cortex, and the dorsal medial geniculate nuclei for the auditory cortex). Intracortical spread of synchrony would also be promoted by the widespread collateralization of layer V corticothalamic cells within the cortex itself. In this scheme, involving the systematic recruitment of cortical and thalamic cells by thalamic matrix cells and layer V corticothalamic cells, large-scale, coherent activity would be set up throughout large regions of cortex in response to an externally or internally generated stimulus. Such coherent activity would provide temporary functional links between discrete populations of cortical and thalamic cells that are broken as an oscillation fades but could be re-formed in new patterns in response to new external or internal influences.

The scheme and the progression of events just outlined has relevance to current views on the involvement of high-

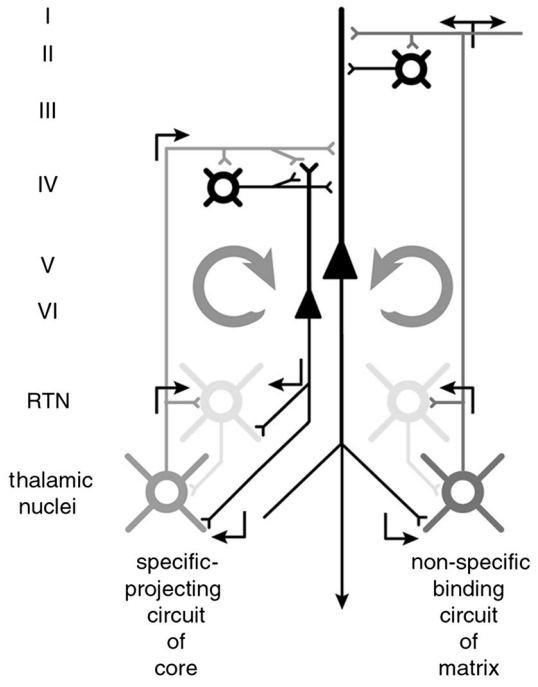

Figure 11. The differential laminar terminations of matrix and core cells form a coincidence detection circuit for cortical pyramidal cells. Synchronous, high-frequency inputs from core and matrix cells would be integrated over the dendritic tree and promote synchronous activity in the cortical cells. Synchrony of larger groups of neurons would be promoted by feedback to the initiating thalamic nucleus by layer VI corticothalamic cells, by widespread extent of matrix cell terminations in the cortex and by widespread distributions of layer V corticothalamic axons in the thalamus. From Jones (2001*b*). Based, in part, on Llinás & Paré (1997).

frequency synchrony in the thalamocorticothalamic network which may serve to unite discrete populations of cortical cells temporarily as part of the process that ensures binding of distributed components of a sensory percept into a single experiential event (Gray *et al.* 1989, 1990; Singer & Gray 1995; Engel *et al.* 1997; Singer 1999; Llinás *et al.* 1998). Stimuli generated naturally in the external world, or experimentally by artificial stimulation of a major subcortical afferent pathway, commonly lead to synchronous, high-frequency discharges in the 20–50 Hz ('40 Hz') range in discrete populations of thalamic relay neurons (Gray *et al.* 1989; Usrey & Reid 1999), and stimulus-dependent, high-frequency oscillations can be correlated between geniculate and visual cortical cells (Sillito *et al.* 1994; Singer & Gray 1995; Neuenschwander & Singer 1996; Castelo-Branco *et al.* 1998; Rager & Singer 1998; Singer 1999), as well as between relay neurons and their cortical projection area in other systems (Timofeev & Steriade 1997).

As indicated above, sub-threshold oscillations of membrane potential in the 20–50 Hz range occur when thalamic cells are depolarized (Steriade *et al.* 1996*a*,*b*) and in the relay nuclei it is these oscillations that can lead to repetitive high-frequency discharges under the influence of afferent driving (Nuñez *et al.* 1992; Singer & Gray 1995; Usrey & Reid 1999). Natural and experimentally induced high-frequency oscillations between a cortical area and its thalamic relay nucleus are synchronized by the corticothalamic projection (Sillito *et al.* 1994; Contreras *et al.* 1996; Steriade & Amzica 1996; Golshani & Jones 1999). Coherency of fast (20–40 Hz) activity in the cerebral cortex and thalamus has been demonstrated by multi-site recording of field potentials and intracellular activities in different neocortical areas (Steriade & Amzica 1996; Steriade *et al.* 1996*a*) and within thalamic nuclei connected with these areas by thalamocortical and corticothalamic connections (Steriade *et al.* 1996*b*).

In the cortex, the synchronization of fast rhythms set up under experimental conditions is spatially limited, but this is consistent with the observation that high frequency cerebral oscillations accompanying cognitive events tend to engage areas of cortex that, although large, are regionally restricted. In the cortex of awake humans, 40 Hz activity, as revealed in magnetoencephalographic traces, is regionally restricted but moves across the cortex as new areas are recruited during a discrete conscious event (Ribary *et al.* 1991). The progression and the time-course taken are consistent with the temporal pattern that would be predicted for the recruitment process envisaged above. The predicted spread of activity in the network is also consistent with the time-course of peripherally elicited or internally generated sensory experiences (Desmedt & Tomberg 1994; Tononi & Edelman 1998; Llinás *et al.* 1998). The capacity of the layer V corticothalamic projection to bring activity in one cortical region to thalamic nuclei that project to adjacent regions, and even to distant regions located in other lobes of the cerebral hemisphere, could extend the binding process by providing a basis for unifying activity in the somatosensory and motor cortex during movement performance (Ribary *et al.* 1991; Murthy & Fetz 1992, 1996*a*,*b*; Sanes & Donoghue 1993), and in parietal areas engaged in perception with that in frontal areas engaged in planning strategies for action (Tononi *et al.* 1992; Lumer *et al.* 1997). Corticocortical connections undoubtedly play a prominent part here as well but they would run parallel to a system of corticothalamocortical loops in spreading activity across the forebrain.

In the scheme outlined here, the collective oscillation of the thalamus and cerebral cortex that accompanies the alerting of the cortex to a new sensory event, and the binding of stimulus features into a global percept as an accompaniment of the act of cognition, depends upon the capacity for activity generated locally in a thalamic nucleus and the cortical area to which it projects to be distributed across large-scale populations of cortical and thalamic cells through the integrated activity of thalamic matrix cells and corticothalamic cells with widespread connections. These should not, however, be construed as a system that is entirely independent of the precisely ordered core cells and the more focused connections of layer VI corticothalamic cells, for the two are highly overlapping and it is unlikely that activity in one system can proceed without integrated activity in the other.

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GLOSSARY

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APV: DL-2-amino-5-phosphonovaleric acid
CNQX: 6-nitrogen,7-cyanoquinoxaline-2,3-dione
EPSC: excitatory postsynaptic current
EPSP: excitatory postsynaptic potential
GABA: γ-amino butyric acid
IPSP: inhibitory postsynaptic potential
NMDA: *N*-methyl-D-aspartate
RTN: reticular nucleus
VPN: ventral posterior nucleus