SYMPOSIUM REPORT

Excitatory and inhibitory connections show selectivity in the neocortex

Jo Watts and Alex M. Thomson

Department of Pharmacology, The School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, UK

The cerebral cortex is pivotal in information processing and higher brain function and its laminar structure of six distinct layers, each in receipt of a different constellation of inputs, makes it important to identify connectivity patterns and distinctions between excitatory and inhibitory pathways. The 'feedforward' projections from layer 4–3 and from 3–5 target pyramidal cells and to lesser degrees interneurones. 'Feedback' projections from layer 5–3 and from 3–4, on the other hand, mainly target interneurones. Understanding the microcircuitry may give some insight into the computation and information processing performed in this brain region.

(Received 6 October 2004; accepted 9 November 2004; first published online 11 November 2004)
Corresponding author J. Watts: Department of Pharmacology, School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, UK. Email: joanne.watts@ulsop.ac.uk

A major afferent input to primary sensory regions of the cortex is from the thalamus. Ascending thalamocortical input arrives in layer 4 (and layer 6) whence it is relayed to layer 3 and from layer 3 onto layer 5 and from layer 5 to layer 6 (Gilbert, 1983; Gilbert & Wiesel, 1985; Bode-Greuel *et al.* 1987). The afferent input is excitatory but rapidly induces disynaptic inhibition which limits the excitation in a spatial and temporal fashion (Porter *et al.* 2001). The majority of the input to the neocortex, however, comes from the cortex. This corticocortical communication consists of both 'feedforward' and 'feedback' projections and much information has been gleaned from studies of the visual cortex in particular. In cat longer-distance, interareal 'feedforward' projections from primary sensory regions to the posteromedial lateral suprasylvian cortical area target layers 3 and 4 (Lowenstein & Somogyi, 1991), forming an input analogous to the primary sensory input to layer 4 in area V1 of the visual cortex, while 'feedback' projections target layers 1, 3 and 6 (Rockland & Drash, 1996). This simplified view has generated much interest in elucidating which excitatory and inhibitory cells target each other and whether there is any interlaminar selectivity. Dual and triple intracellular recordings with biocytin labelling were used to explore small circuits of synaptically connected neurones in slices of adult rat and cat neocortex.

This report was presented at The Journal of Physiology Symposium in honour of the late Eberhard H. Buhl on Structure/Function Correlates in Neurons and Networks, Leeds, UK, 10 September 2004. It was commissioned by the Editorial Board and reflects the views of the authors.

Excitation

Excitatory neurones account for approximately 80% of the neocortical neuronal population and can be divided into two types, pyramidal cells in all layers and spiny stellate cells in layer 4. Most mammalian pyramidal neurones have a number of features in common. These include spiny dendrites, a stout radially orientated apical dendrite that forms a terminal tuft, a set of basal dendrites, an axon descending to the subcortical white matter, a number of intracortical axon collaterals and terminals establishing synaptic contacts of the round vesicle/asymmetric variety. Spiny stellate cells share many features with pyramidal cells but lack a prominent apical dendrite. These neurones use the excitatory amino acid glutamate as their neurotransmitter (Nieuwenhuys, 1994). Buhl *et al.* (1997) published some seminal work pertaining to the pyramidal collateral activation of interneurones and a discussion of what is currently known about intracortical interlaminar excitatory connections and the structure of the cells observed is outlined below.

Excitatory projections from layer 4

The axons of layer 4 spiny excitatory cells project to layer 3 in a focused fashion with long horizontal oblique branches within layer 4 that can also extend into layer 3. They also send less extensive, more tightly focused projections to the deeper layers in all species studied (Lund, 1973; Valverde, 1976; Parnavelas *et al.* 1977; Feldman & Peters, 1978; Gilbert & Wiesel, 1979; Gilbert, 1983; Burkhalter, 1989; Anderson *et al.* 1994). An observation of this

 DOI: 10.1113/jphysiol.2004.076984

laboratory is that layer 4 pyramidal axons ramify more extensively than spiny stellate axons in layer 6 (A. P. Bannister, unpublished observation). In species where there are clear sublaminar divisions, the projections from layer 4 spiny cells are often sublayer specific in both their origin and the termination of axons. In primate visual cortex, upper layer 4Cβ and lower 4Cα cells project to layers 3B and 4A, while upper layer 4Cα neurones project to layer 4B. Layers 4A and 4C send weak projections to layer 5A, while layer 4B, the sublayer that receives no thalamocortical input, sends projections to layers 3A and 2 (Lund, 1988). Only one example of a layer 3 interneurone innervated by spiny layer 4 cells has been identified in cat and one in rat. The cat inhibitory cell was an unusually large basket-like interneurone that had long, horizontal axonal branches in layer 3 and a single branch projecting through layer 4 to form a small, dense terminal arbour in layer 5. Apart from a small population of interneurones therefore, 'feedforward' excitatory connections from layer 4 to layer 3 are largely onto pyramidal targets. Moreover, the majority of terminations are on to the basal dendrites of layer 3 pyramidal cells (A.P. Bannister, unpublished observations).

Excitatory projections from layer 3

It was studies of the projections from layer 3 that provided the first clear evidence that there was interlaminar target selectivity. The descending axons of layer 3 pyramidal cells ramify extensively in layers 2/3 and 5, passing through layers 4 and 6 but rarely forming collaterals there (Spatz *et al.* 1970; Gilbert & Wiesel, 1983; Burkhalter, 1989; Kisvarday *et al.* 1990; Lund *et al.* 1993; Yoshioka *et al.* 1994; Kritzer & Goldman-Rakic, 1995; Fujita & Fujita, 1996). In fact, the probability of finding a connection between a layer 3 pyramidal cell and a large layer 5 cell is extremely high (Thomson & Bannister, 1998; Thomson *et al.* 2002), higher than any other type of pyramid–pyramid connection yet described in neocortex. Figure 1 shows two reconstructions of typical presynaptic layer 3 pyramids and postsynaptic layer 5 neurones. A striking observation from these studies was that layer 3 pyramids appear never to target small, regular-spiking pyramidal cells in layer 5. These cells rarely have apical dendrites extending past layer 4 or lower layer 3 and, as such, cannot receive inputs in layer 1, one of the targets of corticocortical 'feedback' projections from higher order areas (Rockland & Drash, 1996). In contrast, large burst-firing cells of layer 5 receive inputs in layer 1 directly via their own apical dendrites and indirectly via their inputs from layer 3. This may indicate that the large layer 5 cells are a major processing unit since they receive excitatory input both from thalamic sources and higher order cortical areas.

Despite a lack of layer 3 to layer 4 pyramidal excitatory cell connections, layer 3 pyramidal axons do not avoid layer 4 neurones altogether. Interneurones in upper layer 4 are as frequently innervated by layer 3 pyramidal cells as by layer 4 spiny stellate cells. These interneurones displayed a wide range of morphologies and included both proximally targeting basket cells and dendrite-preferring neurones (Thomson *et al.* 2002). Layer 3 pyramidal cells thus select one type of excitatory cell target in layer 5 and inhibitory cell targets in layer 4.

Excitatory projections from layer 5

Layer 5 pyramidal axons contact other pyramids and interneurones within layer 5 and this is where their axons arborize most densely, but they also send projections to all other layers in rat (Burkhalter, 1989; Keller, 1993) and primate (Yoshioka *et al.* 1994; Fujita & Fujita, 1996). Presynaptic layer 5 pyramidal cells that are hundreds of microns from their pyramidal targets innervate more distal regions (Deuchars *et al.* 1994), while those that are close neighbours contact basal and/or apical oblique dendritic branches (Markram & Tsodyks, 1996; Markram *et al.* 1997). Connections from layer 5 pyramidal to layer 3 pyramidal cells are extremely rare. When such connections have been observed they were very weak i.e. there are very few synaptic boutons involved (light microscopic findings) and the cells were displaced further laterally than the powerful descending connection from layer 3–5 (Thomson & Bannister, 1998). There are, however, excitatory inputs from layer 5 to interneurones in layer 3 (Thomson *et al.* 1996; Callaway, 2002). As mentioned previously, thalamocortical input arrives in layer 4 onto first order cells where it is relayed to second order cells in layer 3 and from there to layer 5. The target selections made by pyramidal cells in layers 3, 4 and 5 indicate that the responses of first order cells would remain uncontaminated by excitatory innervation from second or third order excitatory cells but tuned by 'feedback' inhibition. This concept has been demonstrated *in vivo*. In cat visual cortex, first order layer 4 cells responded rapidly to the unsophisticated stimuli that readily activate lateral geniculate nucleus (LGN) cells, the thalamic gateway from the optic nerve. The same stimulus failed to elicit responses from layer 3 cells, showing that the second stage of cortical processing differs markedly from the first (Hirsch *et al.* 2002). In another study of the cat visual cortex, however, it has been demonstrated that, while both X- and Y-type axons from the LGN have been shown to synapse on the dendrites of spiny stellates in layer 4, Y axons also establish many contacts on the basal dendrites of layer 3

pyramids. The somata in layer 4 in synaptic contact with these afferents from the LGN were all shown to be GABA immunopositive, possibly indicative of an inhibitory role, while the somatic targets of X axons were found to be significantly smaller than those of Y axons (Freund *et al.* 1985). The authors postulated that the X and Y subsets selectively target different types of interneurone. These results may also indicate that both direct and disynaptic excitation may cooperate in the coordination of layer 3 responses.

Excitatory projections from layer 6

Layer 6 does not receive densely ramifying projections from the more superficial layers but weak, tightly focused inputs from all other layers. Layer 6 corticocortical pyramidal cells have long horizontal and oblique axon collaterals confined to the deep layers (Zhang & Deschenes, 1997), while the axons of corticothalamic layer 6 cells have ascending collaterals that arborize densely in layer 4 (Gilbert & Wiesel, 1979). Figure 2 shows a reconstruction of a layer 6 corticothalamic-like cell targeting a layer 5

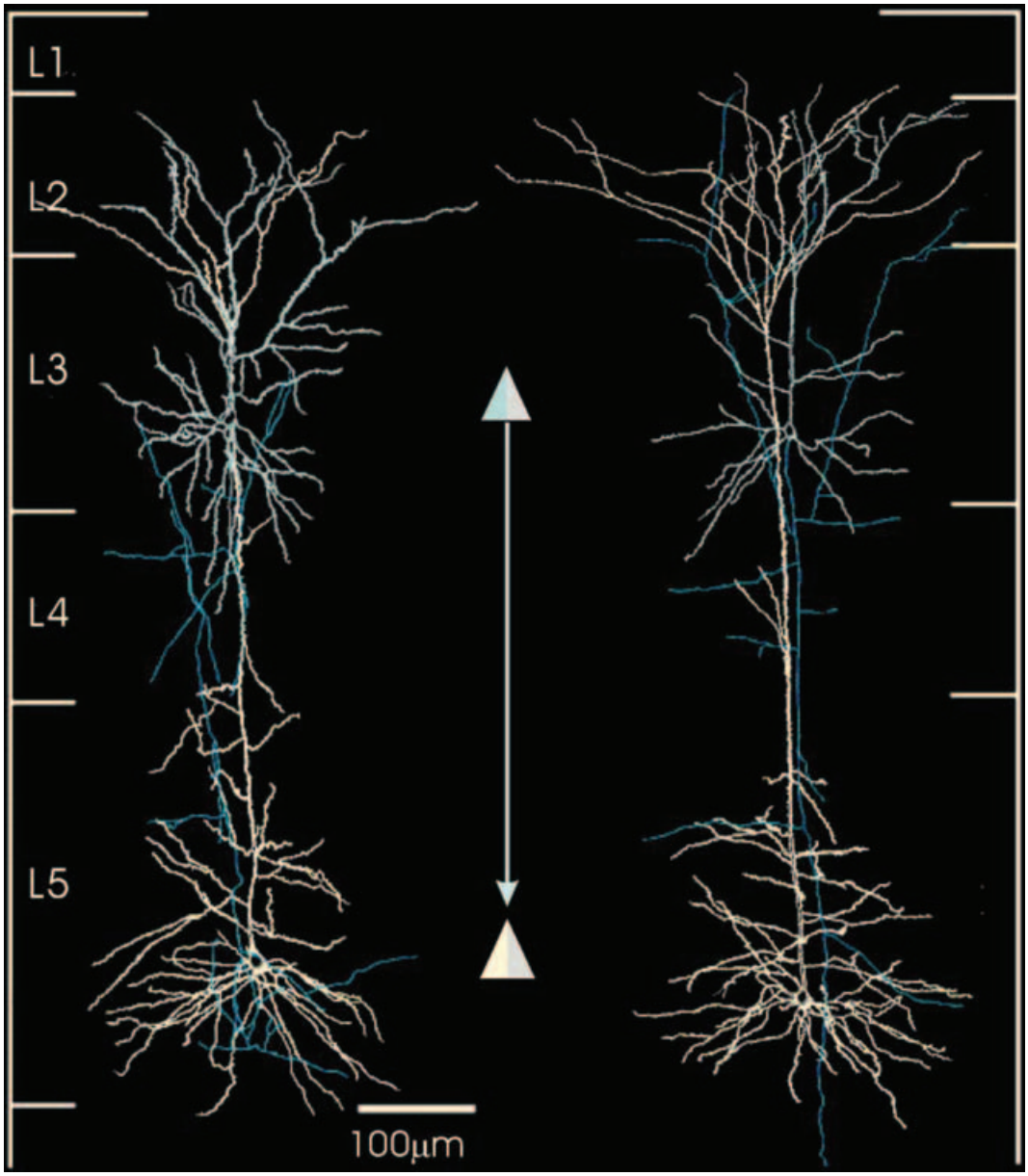

Figure 1. Two examples of layer 3 to layer 5 pyramid–pyramid connections in rat visual cortex
In these connections the presynaptic soma is always very near, within 50 μm, of the postsynaptic apical dendrite and the two neurones have apical dendritic tufts in the most superficial layers that overlap in space. In these pairs, the postsynaptic layer 5 neurone was always a large, burst firing pyramidal cell, never a small pyramidal cell, with an apical dendrite that terminated in layer 4 or layer 3 (adapted from Fig. 4 of Thomson & Bannister, 1998).

interneurone. It appears that each class of pyramidal cell in layer 6 has its own preferred targets, one innervating interneurones in layers 4, 5 and 6, the other pyramidal cells in the deep layers (A. M. Thomson, unpublished observations). Two physiological types of cell have been studied in the cat striate cortex, simple and complex. Simple cells in layer 6 project into layer 4, a layer rich in simple first order cells, while complex cells project to

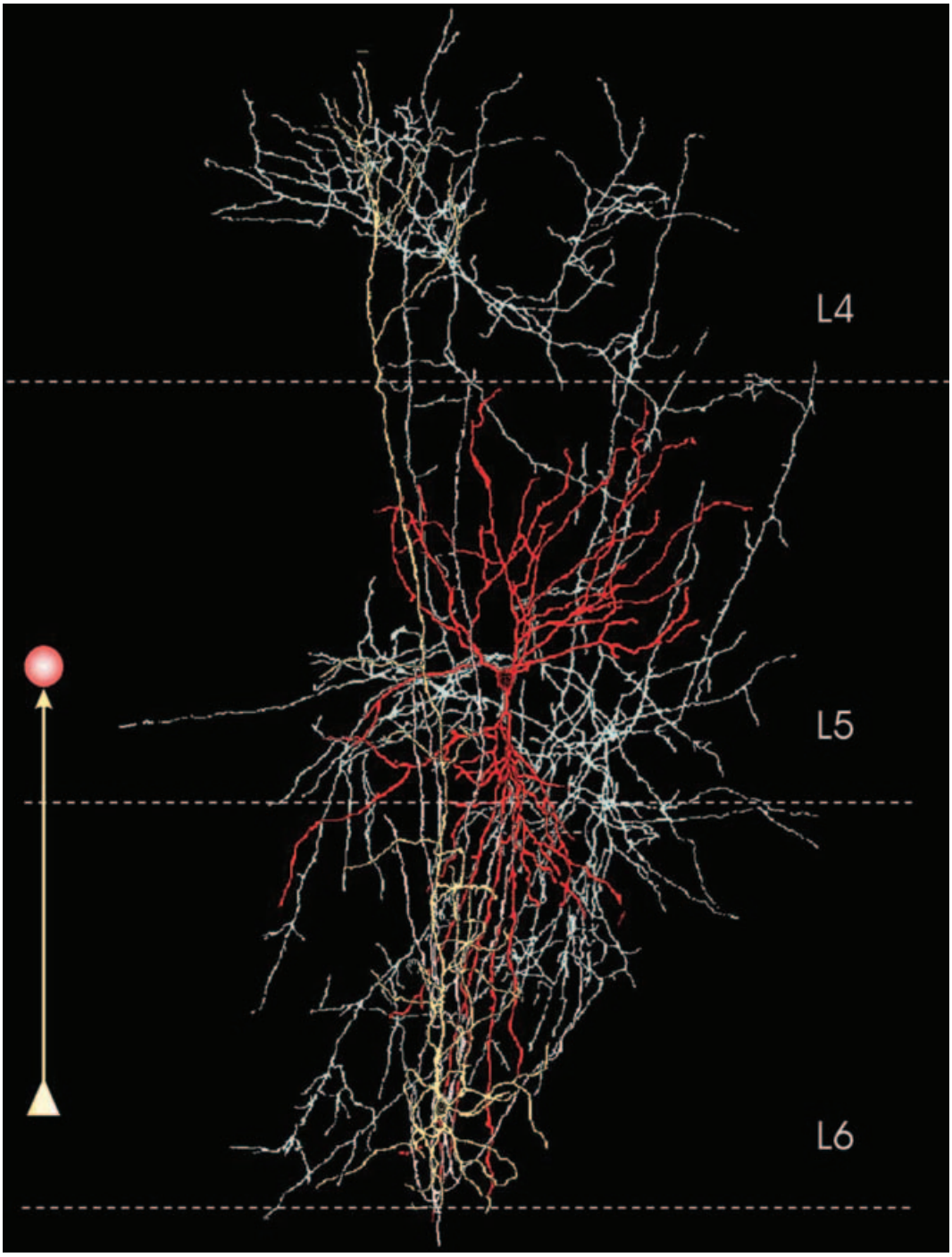

Figure 2. An example of a pyramid to interneurone connection in rat
In this example, the presynaptic layer 6 neurone (yellow soma/dendrites, white axon) was a corticothalamic-like pyramidal cell with an apical dendritic tuft in layer 4. The postsynaptic interneurone (red soma/dendrites, blue axon) was a bitufted, low-threshold spiking, dendrite-preferring interneurone. The interneurone also had an extensive axonal arbour in layer 4. The EPSP elicited by this connection was strongly facilitating with a paired pulse ratio > 3. Despite at least 6 (confirmed ultra-structurally) and possibly up to 12 synapses (visible as close membrane appositions at the microscopic level) mediating this connection, the failure rate in response to the first presynaptic spike of a train was $> 30\%$ (adapted from Fig. 4 of Deuchars & Thomson, 1995*a*).

layers 2 and 3, layers rich in second order complex cells (Hirsch *et al.* 1998).

Inhibition

There is an incredibly diverse population of interneurones in cortical regions – 16 classes have been described in the hippocampus to date (see Somogyi & Klausberger, 2005) and much effort has gone into their classification. In the broadest sense interneurones can be divided into those that target proximal portions of pyramidal cells and those that target their dendrites. The former include axo-axonic cells (chandelier cells; Somogyi, 1977), found in layers 2–6 but more often in superficial layers, and basket cells. The basket cells cover a vast range of sizes and morphologies but include the parvalbumin (PV) containing fast-spiking cells as well as the regular-spiking cells that contain cholecystokinin (CCK) and sometimes vasoactive intestinal polypeptide (VIP; Kawaguchi & Kubota, 1997, 1998; Kubota & Kawaguchi, 1997). Dendrite-preferring cells include double bouquet cells, so-called for their bipolar dendritic arbour, Martinotti cells, most common in deep layers but also found in layer 3 with a characteristic axonal arbour in layer 1, and the late-spiking neurogliaform cells which have dense, convoluted dendritic and axonal arbours that are often concentric (Tamas *et al.* 2003).

While pyramid–pyramid connections and pyramidal inputs to proximally targeting interneurones generally display paired-pulse and frequency-dependent depression (Thomson *et al.* 1993; Thomson & West, 1993), pyramidal input to dendrite-preferring interneurones shows strong facilitation, augmentation and potentiation (Thomson *et al.* 1993; Deuchars & Thomson, 1995*b*; Thomson, 1997; Markram *et al.* 1998; Thomson & Bannister, 1999). This has been most commonly reported in the regular- or burst-firing, somatostatin-containing interneurones (see Reyes *et al.* 1998). The simple prediction from these synaptic properties would be that proximal inhibition would be recruited early in the cortical response to incoming input while dendrite inhibition would only be recruited later, during, or following high frequency activity. What is known about specific interneuronal connections in the cortex is outlined below.

Inhibitory inputs to layer 4

In addition to the interneurones in layer 4 that are innervated by pyramidal cells (and spiny stellate cells) in layers 3, 4, 5 and 6, there are inhibitory inputs to layer 4 from interneurones in other layers. In primates, interneurones in layer 5A innervate all the layers that receive thalamic input (4A, 4Cα and β, 6 and 3) as well as layers 1 and 2 (Lund, 1988). In the rat, some of the layer 5 cells that innervate layer 4 have few or no axon collaterals in other layers. These either resemble small basket or 'clutch' cells with dense, narrow axonal arbours in layer 4 or have a dense local arbour in layer 4 with prominent horizontal, myelinated collaterals over a millimetre in length from which short vertical or oblique branches stem (Thomson *et al.* 1996). Only a small number of layer 3 interneurones and apparently only dendrite-preferring types innervate layer 4, of which the most prominent are double bouquet cells (Somogyi & Cowey, 1981) with a dense local axonal arbour in layers 3 and 4 and a narrower vertical projection into deeper layers (Tamas *et al.* 1998). The majority of proximally targeting layer 3 interneuronal axons do not arborize in layer 4. Layer 3 therefore activates inhibition in layer 4 via excitation of proximally targeting layer 4 interneurones or via dendrite-preferring layer 3 interneurones that arborize in layer 4.

Inhibitory inputs to layer 3

As well as the interneurones in layer 3 that are innervated by pyramidal cells in layers 3 and 5 there are interneurones in other layers that target this layer. Interneurones in layer 4 with a diverse range of morphologies target layer 3B. These include both proximal and distal dendrite-preferring cells. The axons of layer 4 interneurones typically do not extend above layer 3 and rarely penetrate further than layer 3B. In primate, layer 3B receives inhibitory innervation from layer 4C (Lund, 1987, 1988) while in rat and cat the input is from upper layer 4 (Thomson *et al.* 2002). In both rat (Thomson *et al.* 1996) and primate (Lund, 1988) there are two axonal arbours typical of large proximally targeting interneurones in layer 5. The first type have axons that arborize densely in layers 2, 3 and 5 with a single ascending collateral that passes through layer 4 with little or no arborization in that layer. The second, which includes some basket cells and all Martinotti cells, innervate many or all layers between layer 2 (inclusive of layer 1 for Martinotti cells) and layer 5.

Inhibitory inputs to layers 5 and 6

Studies of the primate visual cortex have shown that interneurones of both layer 4Cα and 4Cβ innervate layers 5A and 6, although axons of neither subdivision ramify in layer 5B. There are descending inhibitory projections from layers 3 and 4 to the deeper layers but these tend to be weak and/or focused, although layer 4A has been described as sending strong inhibitory input to layer 5A (Lund, 1988). Most interneurones in layers 3 and 4 either have local axonal arbours that are restricted to the layer of origin or ascending arbours. Those that have descending arbours, however, include double bouquet cells and large basket cells. The former send tightly focused axonal bundles to the deeper layers while the latter send one

or two unbranched myelinated axon collaterals through layer 4 to layer 5 where they generate discrete arbours.

Parallels with the hippocampus?

It is apparent that the question of intralaminar selectivity within the cortex has enormous scope but many details remain undescribed and this is a clear area for future research. It is possible, however, that studies in the hippocampus may be extrapolated to suggest the types of selectivity that will be found in the cortex. The glutamatergic pathways and cells in the hippocampus form the trisynaptic loop. Afferents from the entorhinal cortex synapse onto granule cells, the principal cells of the dentate gyrus. The granule cells send their axons (mossy fibres) to the proximal dendrites of CA3 pyramidal cells. In turn, these cells project to the dendritic regions of CA1 pyramidal cells via Schaffer collaterals. The principal extrinsic projections arise from the CA1 pyramidal cells and terminate in the entorhinal cortex and subiculum, completing the cortico-hippocampo-cortical loop (Freund & Buzsaki, 1996; Vizi & Kiss, 1998). This would be analogous to the proposed situation in the cortex where excitatory input only projects in one direction, from layer 4 to 3 and from 3 to 5, while inhibitory input is bidirectional. The major input to the hippocampus arises from the perforant path. Layer II cells of the entorhinal cortex project to the dentate gyrus and CA3 pyramidal cells (Steward & Scoville, 1976; Tamamaki & Nojyo, 1993) while layer III cells send a parallel projection to the distal dendrites of pyramidal cells in the CA1 subfield and to the subiculum (Hjorth-Simonsen & Jeune, 1972; Steward & Scoville, 1976; Witter *et al.* 1988). Like the cortex, the hippocampus could be seen as a laminar structure but with the three major divisions, the dentate gyrus, CA3 and CA1, lying side by side rather than stacked. The CA subfields display ordered strata largely resulting from the localization of almost all pyramidal cells to a narrow band (stratum pyramidale). Starting from the ventricular surface these strata are stratum oriens, stratum pyramidale, stratum lucidum (in CA3), stratum radiatum and stratum lacunosum moleculare. Inputs to pyramidal dendrites typically stream past at right angles and have been described as making a number of synapses *en passage* (O'Keefe & Nadel, 1978). The local circuit inputs to three classes of interneurone with somata in stratum oriens or stratum pyramidale have been studied in detail. The simple laminar structure of the hippocampus greatly assists the identification of interneurone subclasses. While each class was innervated by neighbouring CA1 pyramidal cells there were differences in the excitatory postsynaptic potential (EPSP) amplitudes and connectivity ratios. The most densely innervated neurones were the oriens lacunosum moleculare (O-LM or horizontal O/A) cells that inhibit the most distal apical dendritic tufts of pyramidal neurones. These cells received excitatory inputs from one in three of the neighbouring pyramidal cells (Ali & Thomson, 1998). Bistratified cells, which innervate the intermediate pyramidal cell dendrites in both stratum oriens and stratum radiatum, coinciding with Schaffer collateral inputs, had inputs from one in seven surrounding pyramids. Basket cells were the least densely innervated and also received EPSPs that were typically smaller than those observed in bistratified cells (Ali *et al.* 1998). The different ratios could be explained by the degree to which each class receives other inputs. O-LM cells are predominantly innervated by CA1 pyramidal cells (Blasco-Ibanez & Freund, 1995) and the horizontal orientation of their dendrites means that they are ideally positioned to contact pyramidal axons as they branch along stratum oriens and the alveus. They are poorly positioned, however, to receive inputs from Schaffer collaterals since O-LM dendrites do not enter stratum radiatum. Bistratified cells have a vertically orientated dendritic tree extending through stratum oriens and stratum radiatum so they are well positioned to receive pyramidal inputs from both CA1 and CA3 but, since their dendrites do not extend into stratum lacunosum moleculare, they do not receive direct input from the perforant path. Basket and chandelier cell dendrites also extend vertically through stratum oriens and stratum radiatum but they also have extensive dendritic arbours in stratum lacunosum moleculare (Freund & Buzsaki, 1996). Since the hippocampus has a simpler laminar structure than the cortex, predictions can be made about the inputs that the classes of interneurone will receive based on the extent and distribution of their dendrites and about their target preferences based on the strata innervated by their axons. Such predictions are not possible in the neocortex because many axonal arbours span several layers, all of which, bar layer 1, contain both the somata and apical and basal dendrites of pyramidal cells and interneurones.

Despite increasingly detailed information about classes of interneurone, it is still not entirely clear why such diversity is necessary. Again studies in the hippocampus may provide some clues. One of the most distinct patterns observed in electroencephalograph (EEG) recordings are the theta oscillations (4–8 Hz) that are often most prominent in the hippocampus, particularly during the exploration of novel environments (Green & Arduini, 1954; Arduini & Pompeiano, 1955; Buzsaki, 2002). These are often accompanied by gamma oscillations (20–80 Hz), prominent during attention/arousal, and it is thought that both rhythms are essential for hippocampal function (Buzsaki & Chrobak, 1995; Lisman, 1999; Fischer *et al.* 2002). *In vivo* studies are beginning to connect activity in different classes of

interneurone with EEG rhythms. In stratum pyramidale, axo-axonic cells were found to fire most during the peak positivity of the theta oscillations (when pyramidal cells fire least) and PV-positive basket cells just after the peak positivity and at the beginning of sharp-wave ripples (120–200 Hz), just before pyramidal cells. O-LM cells and bistratified cells fired at the trough of theta cycles (when pyramidal cells are most active) but O-LM cells were silent during ripple episodes while bistratified cells were active (Klausberger *et al.* 2003). It has been proposed that the PV-positive basket cells provide an inhibitory spatio-temporal structure for large populations of pyramidal cells and that axo-axonic cells synchronize the activity of perhaps thousands of pyramids. Distal dendrite-preferring O-LM cells clearly perform quite different functions. This may indicate that the separate classes of interneurone evolved to coordinate excitatory inputs in specific spatio-temporal patterns depending on the behaviour of the animal.

Although it is possible to predict from these findings when inhibition to the different compartments of CA1 pyramidal cells will be most powerful and that, for example, certain components of proximal and dendritic inhibition will occur at different phases of the theta cycle, it is not yet possible to explain how these different phase relations arise despite a growing body of information about the properties of their local circuit inputs. We clearly need to know much more about the properties of the other excitatory and inhibitory inputs that these interneurones receive. Such explanations are even further from current reality in neocortex and will require a concerted effort to correlate the details that can be studied in *in vitro* preparations with the functionally relevant information that can be obtained *in vivo*.

References

Ali AB, Deuchars J, Pawelzik H & Thomson AM (1998). CA1 pyramidal to basket and bistratified cell EPSPs: dual intracellular recordings in rat hippocampal slices. *J Physiol* **507**, 201–217.

Ali AB & Thomson AM (1998). Facilitating pyramid to horizontal O/A interneurone inputs: dual intracellular recordings in slices of rat hippocampus. *J Physiol* **507**, 185–199.

Anderson JC, Douglas RJ, Martin KA & Nelson JC (1994). Map of the synapses formed with the dendrites of spiny stellate neurons of cat visual cortex. *J Comp Neurol* **341**, 25–38.

Arduini A & Pompeiano O (1955). Electrical activity of a single unit of the hippocampus and changes induced by afferent stimuli. *Arch Sci Biol (Bologna)* **39**, 397–406.

Blasco-Ibanez JM & Freund TF (1995). Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. *Eur J Neurosci* **7**, 2170–2180.

Bode-Greuel KM, Singer W & Aldenhoff JB (1987). A current source density analysis of field potentials evoked in slices of visual cortex. *Exp Brain Res* **69**, 213–219.

Buhl EH, Tamas G, Szilagyi T, Stricker C, Paulsen O & Somogyi P (1997). Effect, number and location of synapses made by single pyramidal cells onto aspiny interneurones of cat visual cortex. *J Physiol* **500**, 689–713.

Burkhalter A (1989). Intrinsic connections of rat primary visual cortex: laminar organization of axonal projections. *J Comp Neurol* **279**, 171–186.

Buzsaki G (2002). Theta oscillations in the hippocampus. *Neuron* **33**, 325–340.

Buzsaki G & Chrobak JJ (1995). Temporal structure in spatially organized neuronal ensembles: a role for interneuronal networks. *Curr Opin Neurobiol* **5**, 504–510.

Callaway EM (2002). Cell type specificity of local cortical connections. *J Neurocytol* **31**, 231–237.

Deuchars J & Thomson AM (1995*a*). Innervation of burst firing spiny interneurons by pyramidal cells in deep layers of rat somatomotor cortex: paired intracellular recordings with biocytin filling. *Neuroscience* **69**, 739–755.

Deuchars J & Thomson AM (1995*b*). Single axon fast inhibitory postsynaptic potentials elicited by a sparsely spiny interneuron in rat neocortex. *Neuroscience* **65**, 935–942.

Deuchars J, West DC & Thomson AM (1994). Relationships between morphology and physiology of pyramid–pyramid single axon connections in rat neocortex *in vitro*. *J Physiol* **478**, 423–435.

Feldman ML & Peters A (1978). The forms of non-pyramidal neurons in the visual cortex of the rat. *J Comp Neurol* **179**, 761–793.

Fischer Y, Wittner L, Freund TF & Gahwiler BH (2002). Simultaneous activation of gamma and theta network oscillations in rat hippocampal slice cultures. *J Physiol* **539**, 857–868.

Freund TF & Buzsaki G (1996). Interneurons of the hippocampus. *Hippocampus* **6**, 347–470.

Freund TF, Martin KA, Somogyi P & Whitteridge D (1985). Innervation of cat visual areas 17 and 18 by physiologically identified X- and Y-type thalamic afferents. II. Identification of postsynaptic targets by GABA immunocytochemistry and Golgi impregnation. *J Comp Neurol* **242**, 275–291.

Fujita I & Fujita T (1996). Intrinsic connections in the macaque inferior temporal cortex. *J Comp Neurol* **368**, 467–486.

Gilbert CD (1983). Microcircuitry of the visual cortex. *Annu Rev Neurosci* **6**, 217–247.

Gilbert CD & Wiesel TN (1979). Morphology and intracortical projections of functionally characterised neurones in the cat visual cortex. *Nature* **280**, 120–125.

Gilbert CD & Wiesel TN (1983). Clustered intrinsic connections in cat visual cortex. *J Neurosci* **3**, 1116–1133.

Gilbert CD & Wiesel TN (1985). Intrinsic connectivity and receptive field properties in visual cortex. *Vision Res* **25**, 365–374.

Green J & Arduini A (1954). Hippocampal electrical activity in arousal. *J Neurophysiol* **17**, 533–557.

Hirsch JA, Gallagher CA, Alonso JM & Martinez LM (1998). Ascending projections of simple and complex cells in layer 6 of the cat striate cortex. *J Neurosci* **18**, 8086–8094.

Hirsch JA, Martinez LM, Alonso JM, Desai K, Pillai C & Pierre C (2002). Synaptic physiology of the flow of information in the cat's visual cortex *in vitro*. *J Physiol* **540**, 335–350.

Hjorth-Simonsen A & Jeune B (1972). Origin and termination of the hippocampal perforant path in the rat studied by silver impregnation. *J Comp Neurol* **144**, 215–232.

Kawaguchi Y & Kubota Y (1997). GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb Cortex* **7**, 476–486.

Kawaguchi Y & Kubota Y (1998). Neurochemical features and synaptic connections of large physiologically-identified GABAergic cells in the rat frontal cortex. *Neuroscience* **85**, 677–701.

Keller A (1993). Intrinsic synaptic organization of the motor cortex. *Cereb Cortex* **3**, 430–441.

Kisvarday ZF, Gulyas A, Beroukas D, North JB, Chubb IW & Somogyi P (1990). Synapses, axonal and dendritic patterns of GABA-immunoreactive neurons in human cerebral cortex. *Brain* **113**, 793–812.

Klausberger T, Magill PJ, Marton LF, Roberts JD, Cobden PM, Buzsaki G & Somogyi P (2003). Brain-state- and cell-type-specific firing of hippocampal interneurons *in vitro*. *Nature* **421**, 844–848.

Kritzer MF & Goldman-Rakic PS (1995). Intrinsic circuit organization of the major layers and sublayers of the dorsolateral prefrontal cortex in the rhesus monkey. *J Comp Neurol* **359**, 131–143.

Kubota Y & Kawaguchi Y (1997). Two distinct subgroups of cholecystokinin-immunoreactive cortical interneurons. *Brain Res* **752**, 175–183.

Lisman JE (1999). Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate–CA3 interactions. *Neuron* **22**, 233–242.

Lowenstein PR & Somogyi P (1991). Synaptic organization of cortico-cortical connections from the primary visual cortex to the posteromedial lateral suprasylvian visual area in the cat. *J Comp Neurol* **310**, 253–266.

Lund JS (1973). Organization of neurons in the visual cortex, area 17, of the monkey (*Macaca mulatta*). *J Comp Neurol* **147**, 455–496.

Lund JS (1987). Local circuit neurons of macaque monkey striate cortex. I. Neurons of laminae 4C and 5A. *J Comp Neurol* **257**, 60–92.

Lund JS (1988). Anatomical organization of macaque monkey striate visual cortex. *Annu Rev Neurosci* **11**, 253–288.

Lund JS, Yoshioka T & Levitt JB (1993). Comparison of intrinsic connectivity in different areas of macaque monkey cerebral cortex. *Cereb Cortex* **3**, 148–162.

Markram H, Lubke J, Frotscher M, Roth A & Sakmann B (1997). Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex. *J Physiol* **500**, 409–440.

Markram H & Tsodyks M (1996). Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature* **382**, 807–810.

Markram H, Wang Y & Tsodyks M (1998). Differential signaling via the same axon of neocortical pyramidal neurons. *Proc Natl Acad Sci U S A* **95**, 5323–5328.

Nieuwenhuys R (1994). The neocortex. An overview of its evolutionary development, structural organization and synaptology. *Anat Embryol (Berl)* **190**, 307–337.

O'Keefe J & Nadel L (1978). *The Hippocampus as a Cognitive Map*. Clarendon, Oxford, UK.

Parnavelas JG, Lieberman AR & Webster KE (1977). Organization of neurons in the visual cortex, area 17, of the rat. *J Anat* **124**, 305–322.

Porter JT, Johnson CK & Agmon A (2001). Diverse types of interneurons generate thalamus-evoked 'feedforward' inhibition in the mouse barrel cortex. *J Neurosci* **21**, 2699–2710.

Reyes A, Lujan R, Rozov A, Burnashev N, Somogyi P & Sakmann B (1998). Target-cell-specific facilitation and depression in neocortical circuits. *Nat Neurosci* **1**, 279–285.

Rockland KS & Drash GW (1996). Collateralized divergent 'feedback' connections that target multiple cortical areas. *J Comp Neurol* **373**, 529–548.

Somogyi P (1977). A specific 'axo-axonal' interneuron in the visual cortex of the rat. *Brain Res* **136**, 345–350.

Somogyi P & Klausberger T (2005). Defined types of cortical interneuron structure space and spike timing in the hippocampus. *J Physiol* **562**, 9–27.

Somogyi P & Cowey A (1981). Combined Golgi and electron microscopic study on the synapses formed by double bouquet cells in the visual cortex of the cat and monkey. *J Comp Neurol* **195**, 547–566.

Spatz WB, Tigges J & Tigges M (1970). Subcortical projections, cortical associations, and some intrinsic interlaminar connections of the striate cortex in the squirrel monkey (*Saimiri*). *J Comp Neurol* **140**, 155–174.

Steward O & Scoville SA (1976). Cells of origin of entorhinal cortical afferents to the hippocampus and fascia dentata of the rat. *J Comp Neurol* **169**, 347–370.

Tamamaki N & Nojyo Y (1993). Projection of the entorhinal layer II neurons in the rat as revealed by intracellular pressure-injection of neurobiotin. *Hippocampus* **3**, 471–480.

Tamas G, Lorincz A, Simon A & Szabadics J (2003). Identified sources and targets of slow inhibition in the neocortex. *Science* **299**, 1902–1905.

Tamas G, Somogyi P & Buhl EH (1998). Differentially interconnected networks of GABAergic interneurons in the visual cortex of the cat. *J Neurosci* **18**, 4255–4270.

Thomson AM (1997). Activity-dependent properties of synaptic transmission at two classes of connections made by rat neocortical pyramidal axons *in vitro*. *J Physiol* **502**, 131–147.

Thomson AM & Bannister AP (1998). Postsynaptic pyramidal target selection by descending layer III pyramidal axons: dual intracellular recordings and biocytin filling in slices of rat neocortex. *Neuroscience* **84**, 669–683.

Thomson AM & Bannister AP (1999). Release-independent depression at pyramidal inputs onto specific cell targets: dual recordings in slices of rat cortex. *J Physiol* **519**, 57–70.

Thomson AM, Deuchars J & West DC (1993). Single axon excitatory postsynaptic potentials in neocortical interneurons exhibit pronounced paired pulse facilitation. *Neuroscience* **54**, 347–360.

Thomson AM & West DC (1993). Fluctuations in pyramid-pyramid excitatory postsynaptic potentials modified by presynaptic firing pattern and postsynaptic membrane potential using paired intracellular recordings in rat neocortex. *Neuroscience* **54**, 329–346.

Thomson AM, West DC, Hahn J & Deuchars J (1996). Single axon IPSPs elicited in pyramidal cells by three classes of interneurones in slices of rat neocortex. *J Physiol* **496**, 81–102.

Thomson AM, West DC, Wang Y & Bannister AP (2002). Synaptic connections and small circuits involving excitatory and inhibitory neurons in layers 2–5 of adult rat and cat neocortex: triple intracellular recordings and biocytin labelling *in vitro*. *Cereb Cortex* **12**, 936–953.

Valverde F (1976). Aspects of cortical organization related to the geometry of neurons with intra-cortical axons. *J Neurocytol* **5**, 509–529.

Vizi ES & Kiss JP (1998). Neurochemistry and pharmacology of the major hippocampal transmitter systems: synaptic and nonsynaptic interactions. *Hippocampus* **8**, 566–607.

Witter MP, Griffioen AW, Jorritsma-Byham B & Krijnen JL (1988). Entorhinal projections to the hippocampal CA1 region in the rat: an underestimated pathway. *Neurosci Lett* **85**, 193–198.

Yoshioka T, Levitt JB & Lund JS (1994). Independence and merger of thalamocortical channels within macaque monkey primary visual cortex: anatomy of interlaminar projections. *Vis Neurosci* **11**, 467–489.

Zhang ZW & Deschenes M (1997). Intracortical axonal projections of lamina VI cells of the primary somatosensory cortex in the rat: a single-cell labeling study. *J Neurosci* **17**, 6365–6379.