Target and temporal pattern selection at neocortical synapses

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We attempt to summarize the properties of cortical synaptic connections and the precision with which they select their targets in the context of information processing in cortical circuits. High-frequency presynaptic bursts result in rapidly depressing responses at most inputs onto spiny cells and onto some interneurons. These 'phasic' connections detect novelty and changes in the firing rate, but report frequency of maintained activity poorly. By contrast, facilitating inputs to interneurons that target dendrites produce little or no response at low frequencies, but a facilitating–augmenting response to maintained firing. The neurons activated, the cells they in turn target and the properties of those synapses determine which parts of the circuit are recruited and in what temporal pattern. Inhibitory interneurons provide both temporal and spatial tuning. The 'forward' flow from layer-4 excitatory neurons to layer 3 and from 3 to 5 activates predominantly pyramids. 'Back' projections, from 3 to 4 and 5 to 3, do not activate excitatory cells, but target interneurons. Despite, therefore, an increasing complexity in the information integrated as it is processed through these layers, there is little 'contamination' by 'back' projections. That layer 6 acts both as a primary input layer feeding excitation 'forward' to excitatory cells in other layers and as a higher-order layer with more integrated response properties feeding inhibition to layer 4 is discussed.

Keywords: cortical information processing; EPSP; paired-pulse depression; interneuron; thalamus; interlaminar connections

1. PATTERNS OF PRESYNAPTIC TRANSMITTER RELEASE

Before a neurotransmitter can be released from a presynaptic terminal, a complex series of interactions between proteins (and lipids) in the vesicular membrane and those in the plasma membrane with the resultant hydrolysis of ATP must occur to prime the synaptic vesicle (see Thomson (2000) and references therein for review). The number of these mature vesicles determines the size of the immediately releasable pool of transmitter at a given active zone and is one of several dynamic variables. Each mature vesicle has a certain probability of being released during an AP. This probability is determined by the local influx of Ca^{2+} and the affinity of the four Ca^{2+} binding sites in the release machinery. These, again, are parameters that are influenced by the preceding activity and dependent upon the proteins expressed at a given active zone and by, for example, their phosphorylation state. Together these three variables determine p, the probability that a given active zone will release a vesicle of transmitter in response to an AP. Having been released, an active zone becomes refractory and does not release again in response to another AP until it has recovered. The terminals of pyramidal axons are typically small and can be envisaged as containing only one active zone, each capable of releasing one (or a very few) vesicles in response to an AP and

becoming refractory after that release. Connections displaying a high p therefore exhibit strong paired-pulse depression as a large proportion of the available release sites (or terminals) are refractory after the first AP. Subsequent EPSPs in a high-frequency train are typically even more strongly depressed and recover more slowly. These, therefore, are phasic synapses, responding powerfully to the start of a presynaptic spike train, modulated by changes in the firing rate, but reporting little about the frequency of continued activity at a given rate (Markram *et al.* 1998*a,b*).

Connections with a low p, however, do not become refractory after a single AP, as very few, if any, of the available release sites have yet discharged a vesicle. Instead they display facilitation that may result from the binding of some, but fewer than the requisite four, Ca^{2+} ions during the first AP. There is therefore a reduced requirement for Ca^{2+} entry during subsequent APs and second EPSPs are facilitated. If the presynaptic neuron fires only one AP, facilitation decays relatively rapidly and after *ca.* 60 ms the next EPSP will, on average, be as small as the first. During trains of presynaptic APs, however, augmentation, which decays more slowly than facilitation, also develops. The adapting firing patterns of pyramidal cells, which result in lengthening interspike intervals as adaptation develops, are still capable, therefore, of maintaining powerfully augmented EPSPs. This is provided that the first interval of a train is brief and that paired pulse facilitation is strongly activated. These connections therefore transmit very little when all presynaptic interspike intervals are long, but respond powerfully to brief bursts of activity. They then 'remember' that brief burst and even the instantaneous

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frequency of the first pair of spikes and continue to be augmented at lower firing rates.

Pyramid–pyramid connections typically display paired-pulse and frequency-dependent depression (Thomson & West 1993; Thomson *et al.* 1993*b*), while pyramidal inputs to some interneurons display powerful facilitation, augmentation and potentiation (Thomson *et al.* 1993*a*, 1995; Deuchars & Thomson 1995; Thomson 1997; Markram *et al.* 1998*a*; Thomson & Bannister 1999). These interneurons include regular- or burst-firing, somatostatin-containing cells that target pyramidal dendrites, while fast-spiking, parvalbumin-containing basket cells typically receive relatively high *p*, 'depressing' connections (Reyes *et al.* 1998) that display a 'notch'. These observations led to the suggestion that the postsynaptic target cell signals its identity to the presynaptic neuron, determining the extent to which each of the many presynaptic mechanisms is expressed in that terminal and thereby ensuring that it receives its own unique transform of the presynaptic spike code.

This is a simplified summary. In reality it is rather more complex and includes a number of additional mechanisms and complex interactions. In some connections, for example, modest facilitation is seen at some frequencies and depression at others. However, the general principles outlined in the previous paragraph hold in both rat and cat neocortex (Thomson & West 2003), that is, that the postsynaptic target neuron selects the patterns of transmitter it will receive from its presynaptic partners. Further details of some of the mechanisms and frequency-filtering capabilities of cortical synapses can be found elsewhere (see Thomson (1997, 2000) for a review). In the context of cortical information processing, a more recently described phenomenon that selectively filters synaptic transmission at gamma frequencies deserves note. This presynaptic mechanism is expressed at most of the 'depressing' connections between spiny excitatory cells and at pyramidal inputs onto parvalbumin immunopositive interneurons in paired intracellular recordings in slices (see figure 1 for parvalbumin immunofluorescence), but not at all depressing connections. These connections exhibit paired-pulse depression at short interspike intervals. Recovery from this depression is at first relatively rapid (time constant ⩽ 10 ms), but is then interrupted by a second, brief phase of depression from which the recovery of the EPSP amplitude is again rapid. As these synapses transmit more effectively both at interspike intervals that are briefer and at intervals that are longer than this second phase of depression, the term 'notch filter' has been coined (Thomson & West 2003). What might such a 'notch' be good for? Synchronous firing of arrays of neurons in phase with the locally generated gamma oscillation is proposed to carry important information in addition to the magnitude of the neuronal response (Singer 1999, 2001). The synchrony appears amongst particular assemblies of neurons at times corresponding with specific components of behaviourally relevant activities (Rhiele *et al.* 2000). The indiscriminate recruitment of many interconnected pyramidal cells into the oscillation would obliterate any signal carried by this subtle code. Mechanisms that act to suppress such indiscriminate recruitment, increasing the salience of functionally meaningful correlations are therefore important.

2. ACTIVATION OF LAYER 4

Thalamocortical afferents arising in specific thalamic nuclei and innervating primary sensory regions of the neocortex target predominantly layer-4 cells, to a lesser degree layer-6 cells and in some regions, 3B cells (see Jones (2001) for a review). Despite its relative numerical weakness (6%; Ahmed *et al.* 1994), the input to layer-4 cells in primary sensory regions appears to dominate layer-4 activity. Local excitatory connections from other layer-4 cells are reported to contribute 28% of the synapses onto spiny layer-4 cells while the ascending axon collaterals of layer-6 corticothalamic pyramidal cells (Zhang & Deschenes 1997) contribute an enormous 45%. The relative impact of these local connections (see figure 3 for a summary) on layer-4 firing may have been underestimated in the past as they are also driven by thalamic inputs.

The relatively dense local connectivity between layer-4 spiny cells (*ca.* 1 : 6 tested pairs were connected) will reinforce inputs that are common to other connected cells, for example, those with similar receptive-field properties. However, these, like many connections between spiny excitatory cells in cortex, are more faithful reporters of the onset of presynaptic activity than of maintained activity. The frequency-dependent depression that dominates the activity of these synapses in adult cats and rats (Tarczy-Hornoch *et al.* 1998; Thomson & West 2003) and in immature rat neocortex (Feldmeyer *et al.* 1999) makes them relatively good detectors of novelty and of changes in the firing rate, but poor reporters of the frequency of maintained activity at any given connection (Markram *et al.* 1998*a*,*b*). The connections from layer-6 pyramidal cells were found to facilitate in one study in the adult cat (Tarczy-Hornoch *et al.* 1998) while, in the immature rat, thalamocortical inputs activated by electrical stimulation are reported to depress even more powerfully than cortico-cortical inputs (Gil *et al.* 1997). It is therefore possible that short, medium and longer term excitatory responses of layer-4 spiny cells to thalamic input are mediated to differing degrees by direct, powerfully depressing thalamocortical inputs, by reinforcing local layer-4 connections, which also depress and facilitate inputs from layer 6, respectively.

Several observations argue against this simple proposal, however. First, in cat visual cortex the responses of layer-4 cells to flashed stimuli did not appear to decay during the period of thalamic activation (Hirsch *et al.* 2002) as might be expected for strongly depressing inputs. Such a decline was seen in the responses of layer-3 cells as might be predicted from the depressing inputs that they receive from layer-4 cells. Second, these thalamocortical terminals are large: large enough to contain more than one release site. Release from another group of large synaptic terminals in cortex, those of fast-spiking basket cells, can maintain release at extremely high frequencies. Some depression is apparent, but it remains to be determined whether the depression during high-frequency trains of IPSPs results from a presynaptic change in release, or a postsynaptic change such as a shift in the Cl$^-$ equilibrium potential and a resultant increase in the proportion of the current carried by HCO$_3^-$. Evidence presented elsewhere in this volume (Bannister *et al.* 2002) indeed indicates that the depression apparent at thalamocortical synapses may
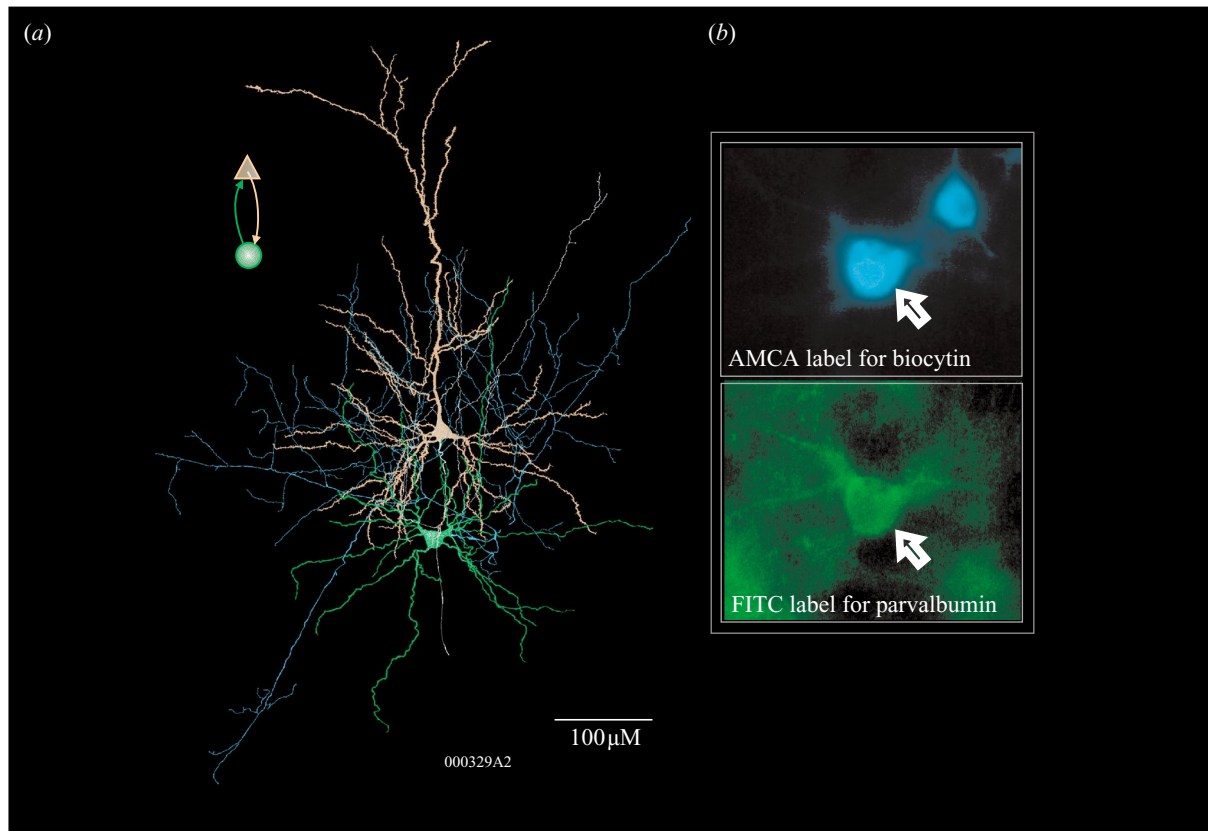
Figure 1. The morphology of a reciprocally connected pyramid–interneuron pair in cat visual cortex. (*a*) A reconstruction of both neurons, with the layer-4 interneuron soma–dendrites in green and its axon in blue. The layer-3 pyramidal soma–dendrites are buff and the axon is white. (*b*) Fluorescent images of the interneuron with AMCA (blue) to reveal the injected biocytin and fluorescein isothocyanate (FITC; green) to label the anti-parvalbumin antibody. Another cell, filled with biocytin during the recording, but not connected, can be seen to the upper right of the interneuron and other, out of focus, parvalbumin immunopositive cells that were not recorded (and not therefore labelled with biocytin) can be seen in the FITC image.

be of postsynaptic, rather than of presynaptic, origin. Clearly, the frequency-dependent characteristics of thalamocortical inputs are an important issue, but one that can probably be satisfactorily resolved only with dual recordings from synaptically connected cells in mature tissue. Finally, if the several components of the response are mediated by different inputs, they are remarkably similarly tuned since the preferred orientations and tuning widths of intracellularly recorded responses to flashed sinusoidal gratings recorded did not change over the duration of the response (Gillespie *et al.* 2001).

3. ROLES PLAYED BY INHIBITION IN CORTICAL CIRCUITS

In all layers from 2 to 6, there are many different types of inhibitory interneurons. Basket cells, which target the somata and proximal dendrites of pyramidal and spiny stellate cells, vary in size from the very small clutch cells with small, very dense axonal arbours restricted to layer 4, to the large layer-4 basket cells. These large cells have long horizontal myelinated axonal branches that form discrete clusters of synaptic boutons up to 1 mm from the soma and are reported to be densely interconnected (Kisvárday 1992). Some also innervate layer-3 cells and in some cases, layer-5 cells (Thomson *et al.* 2002; Thomson & Bannister 2003). The other major group of

proximally targeting interneurons are the chandelier or axo-axonic cells which target the axon initial segments of pyramidal cells (Somogyi 1977). As a major interneuronal recipient of thalamocortical inputs are the parvalbumin-containing cells (Staiger *et al.* 1996) and this group includes many (although not all) basket cells and axo-axonic cells, the interneuronal targets of thalamic afferents in layer-4 cells are likely to provide significant inhibition to the somata, proximal dendrites and axon initial segments of layer-4 spiny cells, both in their immediate vicinity and up to a millimetre away. This proximal inhibition can profoundly affect firing in the target neurons but its functional significance has excited much debate over the years.

A number of roles for proximal inhibition, some relating to the timing of activity and others to the shaping of receptive fields, can be proposed following more recent experiments. In relation to timing, fast-spiking inhibitory interneurons may be amongst the first cells activated in layer-4 cells by a novel thalamocortical input (Swadlow 1994). The very brief time-course of EPSPs in fast-spiking basket cells and the powerful paired-pulse depression typically exhibited by their inputs at high frequencies ensure either that they fire very soon after the start of a given presynaptic spike train, or not at all. Whether they continue to fire during the train depends on several factors. Many fast-spiking, parvalbumin immunopositive inter-

neurons exhibit subthreshold membrane potential oscillations. These become damped during prolonged depolarizations, but are reset, reactivated or boosted by a preceding hyperpolarization such as an IPSP generated by another interneuron (figure 2a), or the fast, deep AHP that follows each AP in these cells (figure 2b). A brief train of interneuronal APs at this frequency (80–100 Hz) can therefore result from a single suprathreshold EPSP (or an IPSP) delivered at a membrane potential within a few millivolts of firing threshold. In addition, if subsequent EPSPs coincide with peaks in these oscillations, the interneuron can be brought to the firing threshold even by strongly depressed EPSPs.

By contrast, the EPSPs in spiny cells are slower to rise and decay and, particularly close to the firing threshold, many have a broad shape that is mediated by NMDA receptor-channels and voltage-gated events. Unless a very large excitatory event that depolarizes the membrane rapidly occurs, they fire rather sluggishly in response to synaptic input. Moreover, the very large fluctuations in size and shape of these EPSPs close to the firing threshold generate a large variability in the latency to firing. The breadth of the EPSPs allows significant temporal summation, however, and even inputs that were subthreshold to start with and that exhibit strong paired-pulse depression can, with temporal summation, reach the firing threshold later in a presynaptic spike train. Added to this, the local axon collaterals of spiny cells are often unmyelinated and therefore slowly conducting, while many basket cells have thick myelinated collaterals. It is therefore perhaps to be expected that local circuit inhibition will be apparent earlier than 'reinforcing' local excitation, particularly perhaps in responses to nonoptimal stimuli. In spiny cells that are recorded intracellularly, the large increases in somatic input conductance that occur early in responses to visual stimulation indicate that the inhibition is powerful, proximal to the soma and attributable to GABA$_A$ receptor activation (Borg-Graham et al. 1998).

This early inhibition could have a number of consequences. First, postsynaptic excitatory cells will be silenced for up to a few tens of milliseconds, depending on the strength of the inhibitory input(s) and their duration. This period of quiescence would allow the outputs of the excitatory neurons to recover, at least partially, from paired-pulse and frequency-dependent depression. When, therefore, these excitatory cells eventually fire, they may transmit more effectively to their postsynaptic targets. Second, the interneurons innervate many cells and, by inhibiting them simultaneously, will increase the probability that they will fire synchronously following the inhibition. The larger interneurons with thick myelinated horizontal axon branches could synchronize the firing of neurons in several columns, even those responding to the more slowly travelling waves of excitatory activity spreading from the column(s) optimally activated by the stimulus (Bringuier et al. 1999). This may help to explain the coincident firing of neurons responding to a nonoptimal but common stimulus (Gray et al. 1989; Engel et al. 1990) and perhaps phenomena such as the perception of faster motion when collinear stimuli are presented (Chavane et al. 2000). Third, the inhibitory interneurons are densely interconnected by chemical (e.g. Tamás et al. 1998; Tarczy-Hornoch et al. 1998; Thomson & Bannister 2003)

and, at least in immature cortex, also by electrical (Gibson et al. 1999; Galarreta & Hestrin 1999) synapses. This dense interconnectivity, together with the inherent properties of fast-spiking interneurons, is proposed to be the substrate for the fast gamma oscillations apparent in the cortical EEG during arousal and attention (e.g. Traub et al. 1996; Bringuier et al. 1997) and in intracellular recordings in vivo (Lampl et al. 1999). Excitatory cells do not typically fire on every cycle of these fast oscillations; their inherent properties are poorly tuned to such frequencies. In addition, the 'notch' reduces the probability of local circuit recruitment at these frequencies. However, correlated, if sporadic, firing between excitatory cells occurs in phase with the oscillations. These interneuronal networks may therefore provide a temporal framework that promotes the correlated firing of assemblies of neurons thought to 'bind' the many facets of a single complex stimulus or behaviour (Singer 1999, 2001). The larger interneurons would help to coordinate the activity of neuronal assemblies in different layers and columns.

Studies in which cortical neurons are recorded intracellularly during responses to visual stimuli demonstrate that subthreshold receptive fields are very much larger than those defined by cell firing (e.g. Chavane et al. 2000). That the subthreshold fields are not simply the vestiges of incomplete developmental reorganization is indicated by the plastic changes that can be produced in suprathreshold fields by repeatedly imposing changes in the covariance between afferent input and cellular response (e.g. Fregnac & Shulz 1999). That receptive-field properties are shaped by inhibitory as well as by excitatory inputs was first demonstrated when the blockade of GABA$_A$ receptors resulted in a broadening of the orientation and length tuning of visual cortical cells (Sillito 1975), and many subthreshold receptive fields also contain large inhibitory domains (Hirsch et al. 1998b; Chavane et al. 2000). That orientation tuning, for example, is not simply due to this inhibition, however, is indicated by the similar orientation preference of excitatory and inhibitory fields in simple cells in the middle layers and by the observation that while excitatory synaptic activity dominates in the centre of the field, it declines in strength away from the centre as inhibition increases (Anderson et al. 2000). This makes sense when the high-energy demands of manufacturing, releasing and responding to a transmitter are considered. To generate selective receptive-field properties simply by imposing a massive inhibitory barrage on top of a powerful excitatory drive would be immensely wasteful. It does not preclude an important role for inhibitory inputs in shaping response properties, but indicates that this may be a more subtle influence and may shift according to conditions and experience.

Inhibition may also play a role in medium to longer term changes in stimulus preference. While repeated coactivation of excitatory inputs (particularly if this includes those, like corticocortical connections, that display a large NMDA receptor-mediated component) can lead to lasting synaptic enhancement, coactivation of inhibitory inputs can, by contrast, lead to lasting synaptic depression (Radpour & Thomson 1991). Repeated presentations of stimuli that activate a cell's inhibitory as well as part of its excitatory domain(s) would be expected to result in depression of those excitatory inputs. Repeated presen-
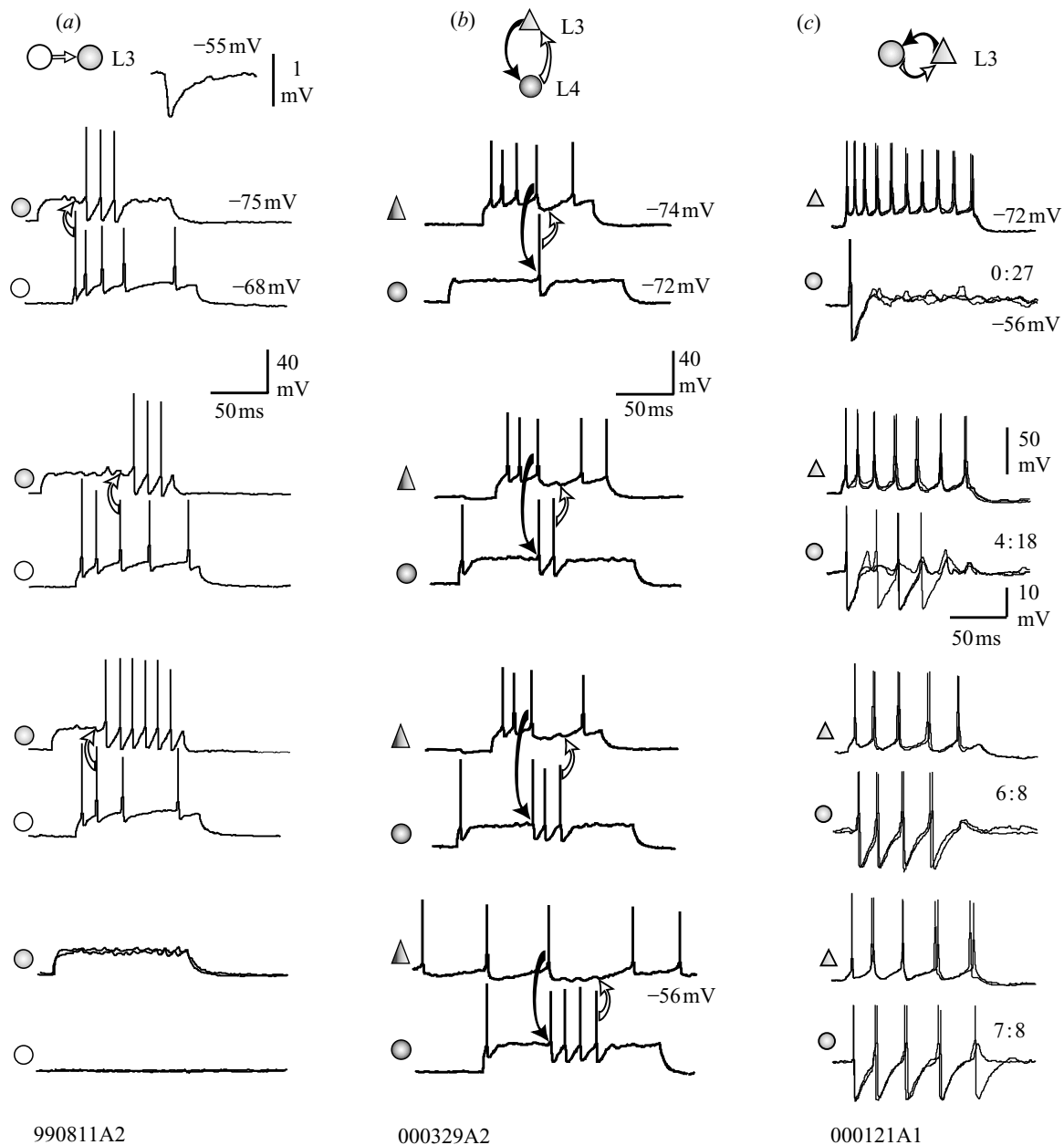
Figure 2. Responses of three synaptically connected cell pairs (*a*–*c*) when both neurons were depolarized close to the firing threshold (current pulses or continuous current injection). The recordings were made with intracellular electrodes in coronal slices of adult neocortex. In each case, one of the neurons was a fast-spiking interneuron (shaded circles in the cartoons) that exhibited spontaneous subthreshold membrane potential oscillations when depolarized. In (*a*), a regular–burst firing interneuron (white circle) elicited a fast IPSP in the fast-spiking cell in rat neocortex (top record). These IPSPs could trigger membrane potential oscillations that brought the postsynaptic interneuron to the firing threshold. The deep spike AHP that followed each AP in the postsynaptic cell could also enhance these oscillations, resulting in brief trains of three to six spikes. Without this IPSP the postsynaptic interneuron exhibited subthreshold oscillations, but these did not reach threshold (bottom records). In (*b*), a layer-3 pyramidal cell (triangle) was reciprocally connected with a layer-4 interneuron in cat neocortex (see figure 1 for morphology). When the interneuron was close to the firing threshold, some of the EPSPs elicited by the pyramidal cell brought the interneuron to firing threshold. The resultant IPSP in the pyramidal cell prolonged the interval to its next AP. Again, the deep spike AHP in the interneuron could trigger membrane potential oscillations and repetitive firing, which in turn elicited a train of IPSPs in the pyramid, further prolonging the pyramidal interspike interval. In (*c*) a layer-3 pyramidal cell was reciprocally connected with a layer-3 interneuron. The membrane potential of the interneuron was adjusted (with constant current injection) so that every first spike EPSP elicited by the pyramidal cell brought it to the threshold. The effect of synaptic depression on the efficacy of transmission at a range of presynaptic firing rates is illustrated. At high rates, the second and subsequent EPSPs were strongly depressed and failed to reach threshold (top records). As the presynaptic firing rate was reduced (from top to bottom) the proportion of second and subsequent EPSPs that reached threshold increased (see ratios above postsynaptic records). In each case several paired records are superimposed (three in each of the top two pairs, two in the lower two pairs). The APs in the interneuron recordings were truncated.
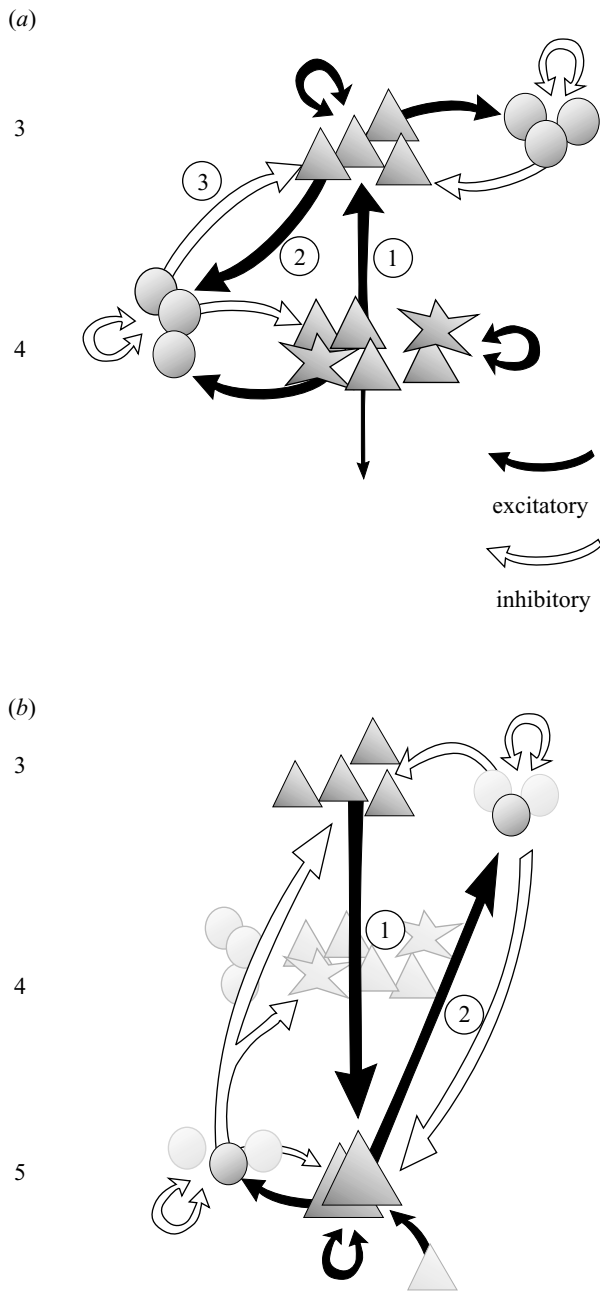
(a)

(b)

Figure 3. A summary of the connections demonstrated within and between layers 3, 4 and 5. (a) Connections involving layers 3 and 4. Excitatory connections from pyramidal cells (triangles) and spiny stellates (stars) are indicated by black arrows, and inhibitory connections from interneurons (ovals) are indicated by white arrows. The connections between layers appear to be more selective and asymmetrical than connections within layers. Layer-4 excitatory cells innervate pyramidal cells in layer 3 (1) but rarely innervate interneurons in this layer. Layer-3 pyramidal cells innervate interneurons, but not excitatory neurons, in layer 4 (2). Layer-4 interneurons frequently innervate pyramidal cells in layer 3 (3), whereas the projections of layer-3 interneurons tend to be confined to layer 3, or to feed forward to layer 2 and layer 5. (b) Connections involving layers 3 and 5. Pyramidal cells in layer 3 innervate large, but not small, pyramidal cells in layer 5 (1). Excitatory projections from layer 5 to 3 are also selective, avoiding pyramidal cells altogether and innervating a subset of layer-3 interneurons (2).
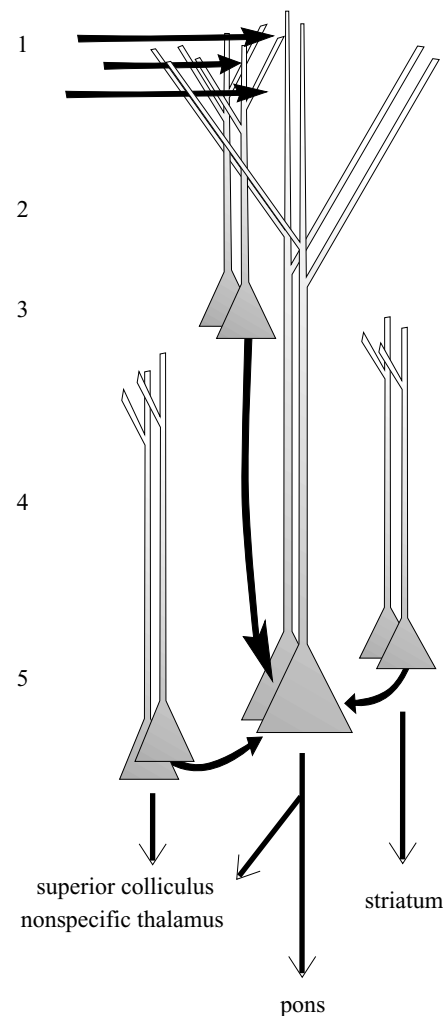

Figure 4. Large and small pyramidal cells in layer 5 receive different inputs. Large layer-5 pyramidal cells have a prominent apical tuft in layer 1 and receive direct excitatory input from layer-3 pyramids that also have a tuft in layer 1. Both these populations can therefore sample inputs to layer 1 from higher cortical areas and nonspecific regions of the thalamus (horizontal arrows). The smaller layer-5 pyramidal cells, by contrast, do not project beyond layer 3, nor do they receive direct excitatory input from this layer and therefore have only very indirect, if any, access to inputs to layer 1. Some of the subcortical projections of layer-5 cells are indicated.

tations of stimuli that result in coincident activation of predominantly excitatory inputs or that resulted in firing, would, however, enhance those inputs. The lasting increases in presynaptic release probability that result from positive pairing paradigms lead to an increase in synaptic efficacy only during the phasic component of a response, with often a decrease during the tonic component (Markram & Tsodyks 1996). The temporal characteristics of the postsynaptic response may therefore be affected more than the overall magnitude of the response. In such a nonlinear system, however, the rate of rise of the EPSP in a pyramidal cell has a dramatic effect not only on the timing of any resultant AP, but on whether an AP is activated at all. Increasing p at several connections that are active simultaneously would be an extremely efficient way of ensuring the recruitment of a postsynaptic pyramid

early in a response. Suppressing p would result in either a delayed activation, or no firing at all. If it can be assumed that the cells activated subsequently are those with similar response preferences and that the inhibition recruited will tend to suppress those with different preferences, a significant alteration in the behaviour of the circuit, with only modest changes in synaptic properties, can be predicted.

Some important questions remain to be addressed: for example, whether specific subsets of interneurons subserve each of these several roles or whether a single interneuron can participate in several, perhaps during different phases of a response, or under different circumstances. There is good evidence for the participation of fast-spiking, proximally targeting interneurons in the generation of fast oscillations and synchrony, but to what extent do these cells also contribute to inhibitory fields? Are these mutually exclusive functions?

4. CONNECTIONS BETWEEN LAYERS 4 AND 3

The responses of neurons in layers 4 and 3 of cat visual cortex to visual stimuli differ significantly, with layer-4 cells responding securely to thalamic input resulting from static flashed stimuli, while responses of layer-2/3 cells did not track these inputs well, but were reliable only in response to richer, for example moving, stimuli (Hirsch *et al.* 2002). In tree shrew area V1, layer-4 cells are not orientation selective and the orientation selectivity in layer-3 cells appears to be generated by convergent input from layer-4 cells displaced along the axis that matches their preferred orientation (Mooser *et al.* 2001). These data indicate that layer-4 cells do not require layer-3 activity to respond effectively to thalamic input, while layer-3 cells integrate a wide range of inputs particularly, perhaps, those from layer 4. The effects of activity in layer 3 on layer-4 cells would, by contrast, be subtle and unable, for example, to impose orientation preference on these cells; this is precisely what might be predicted from the connectivity patterns recently demonstrated between these two layers with dual intracellular recordings *in vitro* (Thomson *et al.* 2002).

Layer-4 spiny excitatory cells (including spiny stellates and pyramidal cells) send focused axonal projections to layer 3 and less extensive, more tightly focused, projections to the deeper layers (Lund 1973; Parnavalas *et al.* 1977; Feldman & Peters 1978; Gilbert & Wiesel 1979; Valverde 1983; Gilbert 1983; Burkhalter 1989; Anderson *et al.* 1994). Paired intracellular recordings in adult rat and cat neocortical slices indicate that the major targets of these ascending axons are pyramidal cells in layer-3B cells. In slices, the probabilities of a layer-3B pyramid receiving input from a layer-4 spiny cell and from a neighbouring layer-3 pyramidal cell are approximately equal (*ca.* 1 : 4 in rat and 1 : 10 in cat) and similar to the within layer connectivity between spiny layer-4 cells (Thomson *et al.* 2002). The axons of the layer-4 spiny cells do not therefore appear to distinguish between potential spiny synaptic targets originating in the two layers. Nor do layer-3 pyramidal dendrites preferentially accept excitatory input from only one of these layers.

This is, however, a one-way connection. None of the pairs tested yielded an excitatory connection from layer 3 to a layer-4 spiny cell. This would perhaps not be surprising if layer 4 did not contain pyramidal cells since layer-3 pyramidal axons ramify extensively in layers 3 and 5, but little, if at all, in layer 4 (or layer 6) (Lorente de Nó 1922; O'Leary 1941; Spatz *et al.* 1970; Gilbert & Wiesel 1983; Kisvárday *et al.* 1986; Burkhalter 1989; Lund *et al.* 1993; Yoshioka *et al.* 1994; Kritzer & Goldman-Rakic 1995; Fujita & Fujita 1996). However, the spiny apical dendrites of layer-4 pyramidal cells ascend through layer 3. Layer-3 pyramidal axons therefore distinguish between the dendrites of pyramidal cells in layer 3 and those originating in layer 4, innervating one and avoiding the other. Alternatively, the dendrites of layer 3, but not those of layer-4 spiny cells, accept excitatory inputs from layer-3 pyramidal axons. That it may be the postsynaptic spiny dendrite that makes this decision, seeking out the inputs it requires, is indicated by their often extremely convoluted shapes and the apparently random lengths and trajectories of their spines. By contrast, the axons of spiny cells (unlike those of most interneurons) have nearly straight trajectories and form predominantly boutons *en passage*.

Interlaminar connections involving interneurons also demonstrated a high degree of selectivity. Only rarely was a layer-3 interneuron activated by a layer-4 spiny cell, the only example identified to date in the cat visual cortex being an unusually large basket-like interneuron with long myelinated horizontal axon collaterals and a single focused arbour in layer 5, but no arborization in layer 4. This cell received excitatory inputs from all three layer-4 spiny stellate cells with which it was tested. It appears therefore that only a minority of layer-3 interneurons are innervated by layer-4 spiny cells, but that those that do receive such inputs are densely innervated. Nor did the majority of layer-3 interneurons innervate layer 4. Many layer-3 interneurons, including most proximally targeting cells, have axonal arbours that are confined to layer 3 or to layers 3 and 2. The major exceptions are the double bouquet cells, which target pyramidal dendrites (Somogyi & Cowey 1984) and whose dense local axonal arbour often spans layers 3 and 4 with the tight bundles of axons typical of this class descending to the deeper layers (Tamás *et al.* 1998). These cells are found in layers 2 to 4 and, like several other types of interneurons that selectively target pyramidal dendrites, are often immuno-reactive for calbindin, calretinin and VIP (DeFelipe & Jones 1992; Conde *et al.* 1994; Del Rio & DeFelipe 1997; Peters & Sethares 1997; Kawaguchi & Kubota 1997). Interneurons containing VIP constitute a major class of thalamorecipient interneurons in layer 4 (Hajos *et al.* 1997). Whether these targets are interneurons that target pyramidal dendrites, for example double bouquet cells, or are basket cells containing VIP and cholecystokinin remains to be determined.

Upper layer-4 interneurons, by contrast, receive significant excitatory input from layer 3 as well as from layer 4 and about half of those in the upper part of layer 4 innervate both upper layer 4 and 3B, though their axons rarely extend beyond 3B (figure 1) (see also Lund (1988) for a review). These cells include both basket cells and interneurons that target dendrites (Thomson *et al.* 2002). If information flow is perceived as passing from layer 4 to layer 3, these findings can be summarized in the following way. 'Forward' interlaminar projections involve both strong excitatory and inhibitory inputs to excitatory neu-

rons, but relatively rare excitatory inputs to inhibitory interneurons; the interneurons in the recipient layer 3 act largely as laminar restricted, local circuit cells with axons and dendrites confined to that layer, or as 'forwardly' projecting cells innervating layer 2, or, in some cases, layer 5 in addition to layer 3. 'Back' projections (from 3 to 4), by contrast, do not activate excitatory cells, but innervate inhibitory interneurons as frequently as do intralaminar excitatory axons, at least in upper layer-4 cells.

The activity of 3B cells is therefore strongly influenced by layer-4 cells, with spiny stellate and pyramidal cells providing a powerful excitatory input, while many upper layer-4 interneurons are well placed to modify layer-3 responsiveness in both temporal and spatial domains. By contrast, the influence that layer-3 cells can have on layer-4 cells is primarily via inhibitory interneurons, via excitation of both layer-4 proximally targeting interneurons and those that target dendrites and via double bouquet cells in layer 3. A significant proportion of the layer-4 interneurons activated by and able to inhibit cells in both layers are parvalbumin immunopositive. It is likely, therefore, that they also receive a significant input from the thalamus (Staiger *et al.* 1996) and coordinate this input with activity in the two layers. The excitatory inputs that they receive from local spiny cells are of the phasic, depressing variety, particularly effective at the start of a response, but their inherent characteristics and mutual interconnectivity can maintain oscillatory activity for tens to hundreds of milliseconds in the absence of additional excitatory input. By contrast, the interneurons that target dendrites often receive low p facilitating inputs whose efficacy increases as the response continues. The effect of these interneurons on spiny cell firing will be less powerful than that of basket cells, but they can shunt inputs to the dendrites that they innervate, more selectively suppressing responses to particular inputs as well as the localized activation of dendritic voltage-gated currents.

5. CONNECTIONS BETWEEN LAYER 3 AND LAYER 5

Connections from layer 3 to 5 and from 5 to 3 can also be seen as 'forward' and 'back' projections, respectively. Extrapolating from the results obtained in layers 3 and 4, the predictions would be that layer 5 would only influence activity in layer 3 subtly and only via inhibition, and that layer 5 would exhibit response properties that were dependent on additional integration, not seen at the level of layer 4 or layer 3. This is indeed what has been found. Orientation tuning curves of the excitatory and inhibitory domains of the receptive fields of layer-3/4 cells in cat visual cortex were very similar (within 7°) while the preferred orientations for these two components of the receptive fields of layer-5 cells were very different (average 54°; Martinez *et al.* 2002).

Layer-3 pyramidal cells innervate large layer-5 pyramidal cells (but not the smaller pyramids) within a narrow 'micro-column' with the highest connectivity ratio yet reported for intracortical excitatory connections, that is, an impressive level of tightly focused convergence (Thomson & Bannister 1998). They also innervate some interneurons (Thomson *et al.* 1996), though few examples have been identified to date. There are also several types

of interneurons with their somata in layers 3 and 4 that innervate layer 5, both basket cells and cells that target dendrites. Typically, these descending interneuronal arbours are much narrower in layer-5 cells than the arbours in the layer of origin, indicating, perhaps, that they contribute to different spatial domains in the two layers. The excitatory 'back' projection from layers 5 to 3, like that from layers 3 to 4, only very rarely contacts layer-3 pyramidal cells (Thomson & Bannister 1998; see also figure 4), but activates interneurons with a regular spiking behaviour (Dantzker & Callaway 2000). Subsets of layer-5 basket cells also project to layer 3 in primates (macaque; Lund 1987, 1988) and in rats (Thomson *et al.* 1996), some innervating layer 4 *en route*, while others arborize only in layers 5 and 3. In addition, Martinotti cells, typically found in the deep layers, have a highly branched, ascending axonal arbour that innervates all layers from the origin to layer 1.

The connections between layers 4 and 5 have yet to be studied in any detail with paired recordings, but the prediction from the above would again be that layer 4 may excite layer-5 pyramidal cells, but that layer-5 pyramidal cells will activate predominantly inhibitory layer-4 interneurons. Interneurons with their somata in layer 5 that densely and sometimes selectively innervate layer-4 cells have also been described in primates (Lund 1988) and in rats (Thomson *et al.* 1996).

6. CONNECTIONS BETWEEN LAYER-5 CELLS AND THE THALAMUS

In relation to the connections between the thalamus and cortex it is of interest to note that the large, burst-firing layer-5 pyramidal cells that receive direct excitatory input from layer-3 cells have an extensive apical dendritic tuft in layer 2/1, as do the presynaptic layer-3 pyramids that innervate them so densely. Thus, both cell groups can receive input in layer 1 (as well as in all layers in between). The major inputs to this layer include 'feedback' from 'higher' cortical areas (Rockland & Drash 1996), and inputs from higher-order thalamic regions (see Jones (2001) for a review). Large layer-5 cells are therefore well positioned to integrate information from several cortical and subcortical sources. They project subcortically to regions such as the superior colliculus and the pons (Wang & McCormick 1993) as well as to higher-order thalamic regions, such as the pulvinar. Layer-5 cells do not, however, innervate the inhibitory thalamic nucleus, nRT or the specific thalamic nuclei (see Jones (2001) for a review). These thalamic nuclei do not therefore receive 'feedback' from layer-5 cells engaging in a high level of integration of many types and levels of information flow. This information is relayed to higher-order regions. The apical dendrites of the smaller, regular spiking pyramids that do not receive direct excitatory input from layer-3 cells rarely extend beyond layer 3 and cannot therefore access layer-1 inputs either directly or via layer-3 cells. Layer 5 clearly includes two parallel information streams therefore that access different information, but which are interconnected via local pyramid–pyramid connections in layer-5 cells (Deuchars *et al.* 1994; Thomson & Deuchars 1997). In upper layer-5 cells these smaller pyramids project, for example, to the striatum (Catsman-Berrevoets &

Kuypers 1978), while those in lower layer 5 project, for example, to the superior colliculus and to nonspecific thalamic nuclei (White & Hersch 1982). In the pulvinar they constitute a prominent source of afferents that are morphologically distinct from those originating in large layer-5 pyramids (Rockland 1996).

7. LAYER 6: EARLY SENSORY PROCESSING OR COMPLEX INTEGRATION?

Should layer 6 be viewed as a thalamorecipient, input layer, with a role in early sensory processing, as an output layer sending highly integrated information to subcortical regions, or does it function in both capacities, perhaps with different types of pyramidal cells subserving different roles? Layer-6 pyramidal cells certainly display a wide range of morphologies that seem to correlate with their cortical and subcortical targets in rat somatosensory cortex (Zhang & Deschenes 1997). The clearest candidates for a role in early sensory processing are those that project to specific thalamic nuclei and send a dense, focused axonal arbour to layer-4 or 3B cells (Gilbert & Wiesel 1979; for sublayer selective arbours see also Wiser & Callaway 1996) where their dendrites also ramify. Simple cells with a similar morphology in upper layer-6 cells of cat visual cortex behaved, like layer-4 cells, as first-order cells responding to stimuli that activated LGN cells (Hirsch *et al.* 1998*a*). It may be these cells that provide the feedback that results in correlated firing of groups of thalamic relay cells aligned to the orientation preference of the cortical column (Sillito *et al.* 1994). Complex lower layer-6 cells displayed either first- or second-order characteristics and projected to other layers that were rich in complex cells, the superficial layers, or layer 5 (Hirsch *et al.* 1998*a*). In rat, corticothalamic lower layer-6 cells that project both to the specific venteroposteriomedial nucleus of the thalamus (but not to nRT) and to the more posterior nonspecific nuclei, Po, were small, short pyramids with apical dendrites terminating in layer 5. Their axonal arbours are broader than those of putative specific corticothalamic cells and ramify in layer 5. Corticocortical cells in layer 6, with a range of nonconventional pyramidal morphologies, also preferentially innervate the deeper layers (Zhang & Deschenes 1997).

The two layer-6 subdivisions may represent the different origins of cells in this layer, with the upper division originating from the cortical plate, while the lower originates from the primordial plexiform layer. Some discrepancies in the literature about the role(s) played by layer-6 input to layer 4, that is, whether it serves primarily an excitatory or an inhibitory role, may result from this dual purpose. From the foregoing discussion, the prediction would be that the first-order, specific thalamocortical cells in upper layer 6 would provide an excitatory forward projection to spiny excitatory and to some inhibitory cells, while the deeper part of the layer would primarily activate inhibition in layer 4, possibly via interneurons in layer 5. Clearly, a much more detailed study of the interlaminar projections from layer 6, particularly to layer 4, is needed.

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GLOSSARY

3B: lower layer 3
AHP: after hyperpolarization
AP: action potential
EEG: electroencephalogram
EPSP: excitatory postsynaptic potential
GABA: γ-aminobutyric acid
IPSP: inhibitory postsynaptic potential
LGN: lateral geniculate nucleus
NMDA: *N*-methyl-D-aspartate
nRT: nucleus reticularis (of the thalamus)
p: synaptic release probability
VIP: vasoactive intestinal polypeptide