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REVIEW

Excitatory signal flow and connectivity in a cortical column: focus on barrel cortex

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Abstract A basic feature of the neocortex is its organization in functional, vertically oriented columns, recurring modules of signal processing and a system of transcolumnar long-range horizontal connections. These columns, together with their network of neurons, present in all sensory cortices, are the cellular substrate for sensory perception in the brain. Cortical columns contain thousands of neurons and span all cortical layers. They receive input from other cortical areas and subcortical brain regions and in turn their neurons provide output to various areas of the brain. The modular concept presumes that the neuronal network in a cortical column performs basic signal transformations, which are then integrated with the activity in other networks and more extended brain areas. To understand how sensory signals from the periphery are transformed into electrical activity in the neocortex it is essential to elucidate the spatial-temporal dynamics of cortical signal processing and the underlying neuronal 'microcircuits'. In the last decade the 'barrel' field in the rodent somatosensory cortex, which processes sensory information arriving from the mysticial vibrissae, has become a quite attractive model system because here the columnar structure is clearly visible. In the neocortex and in particular the barrel cortex, numerous neuronal connections within or between cortical layers have been studied both at the functional and structural level. Besides similarities, clear differences with respect to both physiology and morphology of synaptic transmission and connectivity were found. It is therefore necessary to investigate each neuronal connection individually, in order to develop a realistic model of neuronal connectivity and organization of a cortical column. This review attempts to summarize recent advances in the study of individual microcircuits and their functional relevance within the framework of a cortical column, with emphasis on excitatory signal flow.

Keywords Cortical column · Excitatory signal flow · Canonical circuit · Cortical connectivity · Lemniscal and paralemniscal pathway

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The concept of cortical columns—a historic perspective

A striking feature of the neocortex is its organization into functional columns, a system that is preserved throughout mammalian evolution, from monotremes to primates (Fig. 1A–E). This concept is based on pioneer work by Mountcastle (1957) describing the cortical representation of somatosensory perception. Microelectrode penetrations perpendicular to the pial surface showed that neurons in each cellular layer had similar properties of place (i.e. with similar 'receptive fields') and modality (responsive to similar sensory modalities like skin or proprioception). These neurons were organized in 300–500 μm-sized blocks of neocortical tissue (latter coined cortical columns; reviewed by Mountcastle 1997; see Figs. 1C, 2).

This model was subsequently adopted and corroborated by Hubel and Wiesel (1962, 1963) to describe the functional organization of the visual (striate) cortex into so-called ocular dominance columns. Ocular dominance (see Fig. 1D, E) is the preferential activation of visual neurons following stimulation of either the ipsi- or contralateral eye. Such a columnar organization was also demonstrated for the orientation and direction selectivity of neurons in

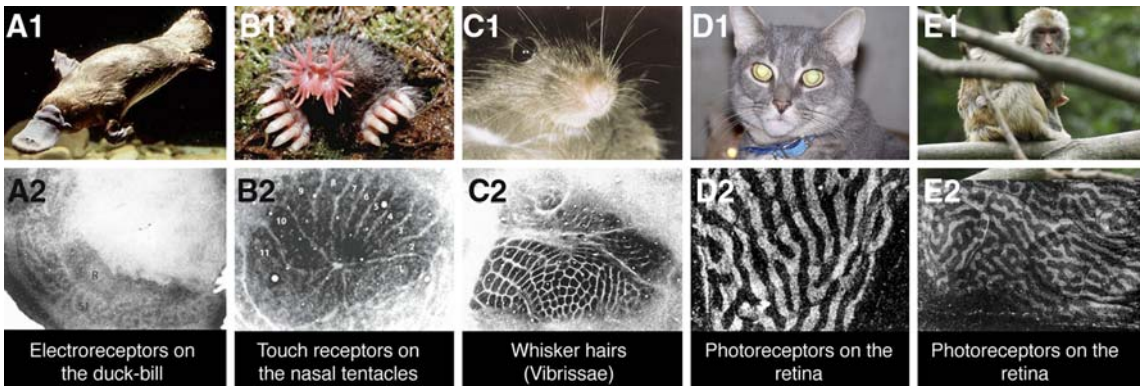


Fig. 1 Conservation of the columnar organisation of sensory cortices throughout mammalian evolution. Already monotremes have a clearly discernible columnar representation of peripheral receptors, shown here for the electroreceptors on the duck-bill (**A1**, **A2**) of the platypus (*Ornithorhynchus anatinus*; reproduced from Pettigrew JD, 2004; J Physiol (Paris) 98:113–124; with permission from Elsevier). Both the night-active Eulipotyphla (represented by the star-nosed mole, *Condylura cristata*; reproduced from Catania KC, 2002; J Neuroctol 31:347–358; with permission from Springer; **B1**, **B2**) and rodents (represented by the house mouse, *Mus musculus*; **C1**, **C2**) show a columnar somatotopic representation of touch and vibration. In carnivores (represented by a domestic cat, *Felis silvestris cattus*; **D1**, **D2**) and primates (represented by a Rhesus macaque, *Macaca mulatta*; **E1**, **E2**) the visual system is organised in ocular dominance columns (**E2**), orientation columns, and the blob vs. non-blob system for *colour* vision

the visual cortex and has also been proposed for colour vision. However, the concept of the columnar organisation of the neocortex has been demonstrated only for sensory cortices but not for other cortical areas.

Many of the different types of neocortical neurons have already been described more than 100 years ago by Ramón y Cajal (1904). However, the morphological and functional properties of the neuronal microcircuitry in which they are embedded are still rather unknown. In a first attempt, Szentágothai (1975) proposed a hypothetical model of neuronal networks within a cortical column based on morphological data that included both principal (excitatory) neurons and GABAergic (inhibitory) interneurons known at the time (Fig. 3). A major drawback of his model circuitry was the limited information concerning the functional properties of individual neurons and their synaptic connections.

Over the last 10 years the so-called 'barrel field' in the somatosensory cortex of rodents have become a quite attractive model to study neuronal microcircuits in a cortical column. The barrel cortex is the cortical representations of the whisker pad on the snout of rodents (Woolsey and van der Loos 1970; see Figs. 1C, 2). In acute brain slice preparations the barrel field can be easily visualized which allows the unequivocal identification of a 'barrel' column, the putative morphological correlate of the cortical column (Fig. 2, right). This is not possible in slice preparations from other sensory cortices such auditory and visual cortex.

In the barrel cortex, a cortical column contains approximately 10,000–20,000 neurons distributed over six laminae (Keller and Carlson 1999). They fall into two major classes: excitatory principal neurons, pyramidal and spiny stellate cells, that constitute 80–85% of the neuronal population providing most of the local, cortico-cortical and extra-cortical projections and a heterogeneous population of GABAergic interneurons, which are generally inhibitory (Cauli et al. 2000; Gupta et al. 2000; Karube et al. 2004; Kawaguchi and Kubota 1997, 1998; Porter et al. 2001; Támas et al. 1998; for a review see Markram et al. 2004; Somogyi et al. 1998) distributed throughout cortical layers 1–6. Inhibitory interneurones shape the flow of excitation and in particular are involved in sharpening the receptive field (for a review see Swadlow 2002). Due to the superposition of many neuronal microcircuits within the columnar network it is necessary to determine structure and function of *individual* synaptic connections to understand the signal processing within a cortical column.

Methods to study connectivity in a cortical column

To date, several approaches exist to directly study neuronal microcircuits and obtain qualitative and quantitative aspects of neocortical connectivity: Dual and more recently multiple microelectrode recordings combined with simultaneous biocytin-fillings in acute brain slices allowed for the first time the correlation of functional and morphological properties of pre- and postsynaptic neurons within defined synaptic connections (Deuchars et al. 1994; Thomson and West 1993; Fig. 4d). Infrared video microscopy combined with patch-clamp recording techniques further facilitated this approach (Dodt and Zieglgänsberger 1990; Stuart et al. 1993). Thus, it was possible to record from visually identified neurons in defined cortical microcircuits with an improved temporal resolution. A few studies also demonstrated that paired recordings are

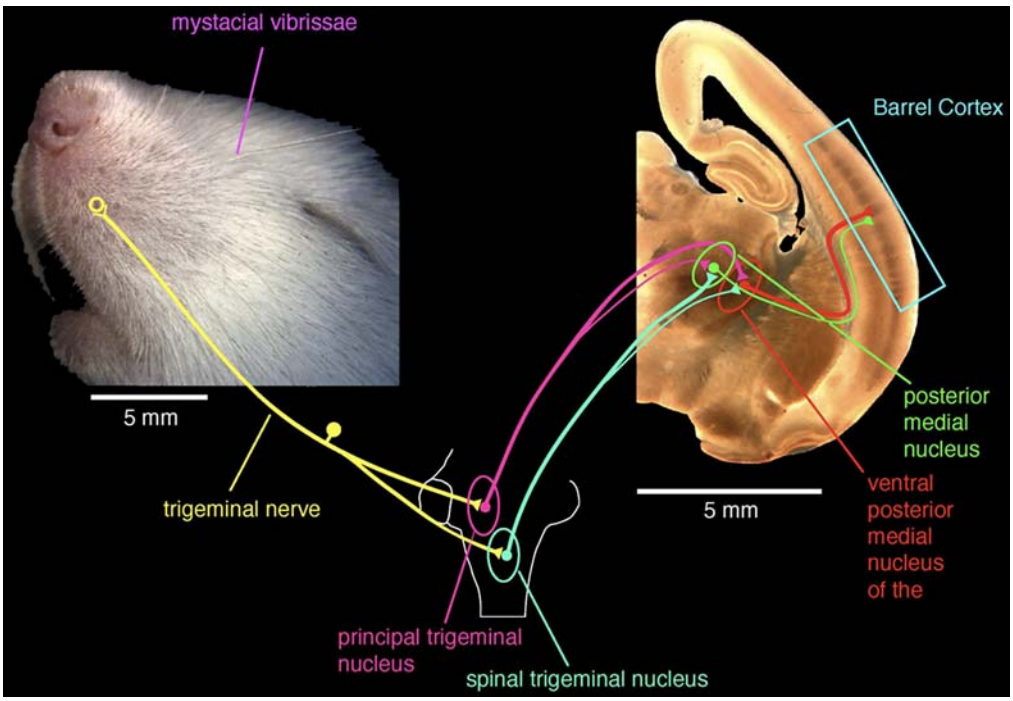


Fig. 2 The whisker to barrel cortex pathway. In rodents the mystacial whiskers are organized in rows and arcs on the snout. Mechanoreceptors at the base of the whisker hairs transduce sensory information, which is first relayed via afferent axons in the trigeminal nerve to different trigeminal relay nuclei in the brainstem, mainly the principal and the spinal nucleus. From there, sensory signals are relayed to the thalamus, and here predominantly to the ventroposterior medial nucleus (*VPM*) and the posterior medial nucleus (*POm*). Finally, thalamic afferents arising either from neurons in the VPM (*red* pathway) or POm project (*green* pathway) project to different cortical laminae in the somatosensory barrel field (*framed area*) of the neocortex

feasible under in vivo conditions (Bruno and Sakmann 2006; Crochet et al. 2005; Matsumura et al. 1996).

Another approach to study neuronal microcircuits are single neuron-recordings combined with photo-release of caged glutamate to stimulate presynaptic neurons originally introduced by Callaway and Katz (1993) was used to investigate cortical connectivity, in particular that of excitatory neurons. This technique allows a rapid scan of putative synaptic inputs to individual neurons over a relatively wide cortical surface (~500 μm), i.e. to assess their connectivity and has therefore now been applied extensively (Boucsein et al. 2005; Bureau et al. 2004, 2006; Dantzker and Callaway 2000; Dodt et al. 2003; Schubert et al. 2001, 2003, 2006; Shepherd and Svoboda 2005; Shepherd et al. 2005; Yoshimura et al. 2005; cap. A-C Fig. 4a–c). However, its spatial resolution is limited and synaptic dynamics, short and long-term synaptic plasticity, the number and nature of synaptic inputs and the type of presynaptic neuron cannot be unequivocally identified. Thus, to describe the functional and structural connectivity in the neocortex in detail a combination of the paired recording and photostimulation techniques would be desirable, but has not yet been achieved.

Furthermore, so-called 'optical probing' techniques have been used to identify neuronal microcircuits in the neocortex. Here, neurons are stimulated while a population of other neurons (loaded with calcium indicator dye) are imaged for calcium signals (Kozloski et al. 2001; Peterlin et al. 2000). Calcium signals at short latency indicate a monosynaptic connection. A variant of this technique is the 'reverse optical probing' or 'ROPing' (Aaron and Yuste 2006): calcium imaging of a neuronal population is combined with intracellular patch-clamp recordings. Presynaptic neurons are not stimulated but spontaneous synaptic activity of postsynaptic neurons is recorded. A reverse correlation analysis is performed to detect presynaptic neurons that fire action potentials time-locked with recorded synaptic events. While both optical probing techniques allow the assessment of monosynaptic connections even over a wide cortical surface (Kozloski et al. 2001), the morphological properties of only one neuron (either post- or presynaptic) in the connection can be studied. In addition only limited information concerning functional properties of the connection can be obtained.

Excitatory signal flow in the barrel cortex

Neuronal connectivity, the reliability and efficacy of synaptic connections together with morphological characteris-

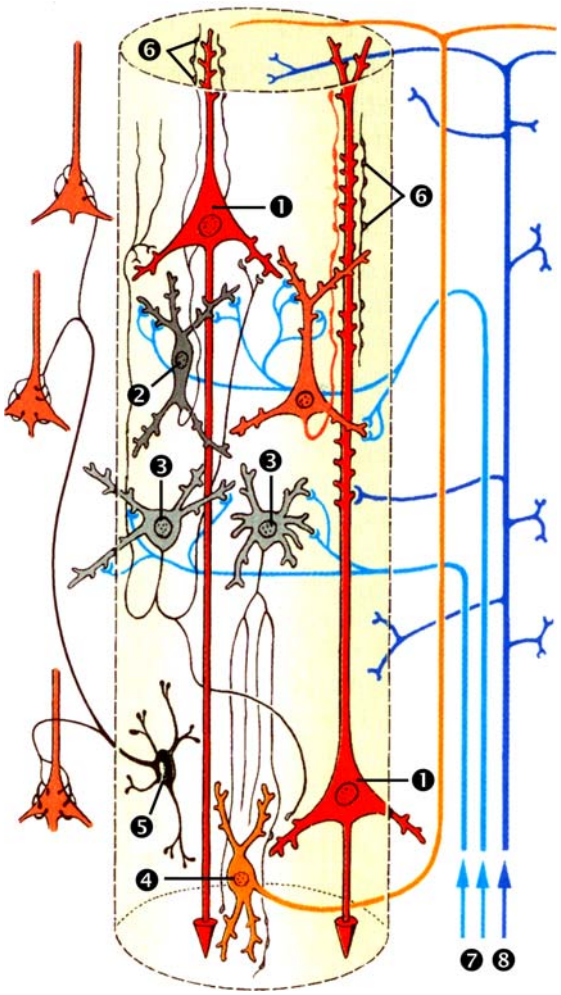


Fig. 3 Simplified model of a cortical column. First hypothetical model of neuronal networks within a cortical column based on morphological data that included both principal, excitatory neurons and inhibitory GABAergic interneurons known at the time. Abbreviations (❶) pyramidal neurons in layers 2/3 and 5; (❷) double bouquet cell; (❸) spiny stellate neurons in layer 4; (❹) Martinotti cell in layer 6; (❺) basket cell in layer 5 establishing axo-somatic contacts with pyramidal neurons; (❻) *en passant* axons of double bouquet cells establishing synaptic contacts on apical dendrites of pyramidal neurons. (❼) Thalamic afferents; (❽) associational fibres (modified from 'Taschenatlas der Anatomie' Thieme Verlag, Stuttgart/New York, 2001, with permission)

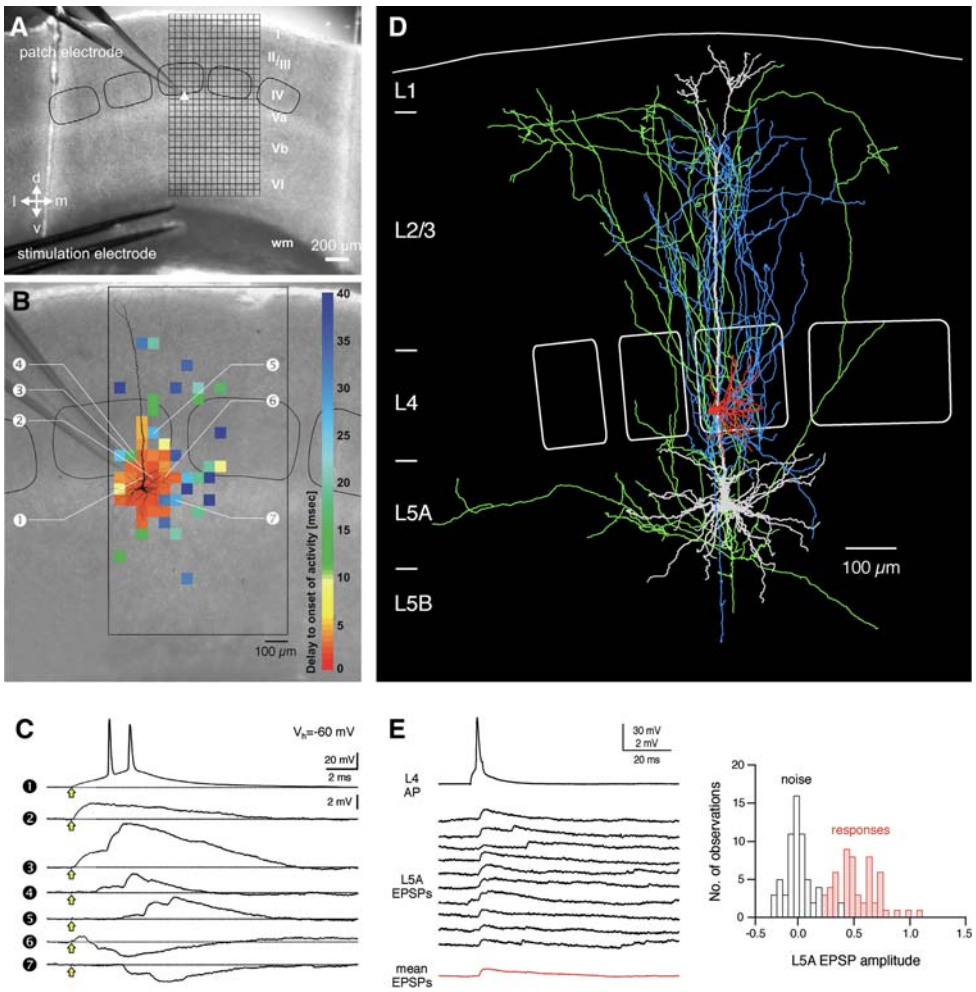
tics of the excitatory neurons such as the extent of their dendritic arbour, their axonal projection pattern and the number and location of synaptic contacts (Figs. 5, 9) determine the flow of excitatory signals in the cortical column. Within the barrel column, specific synaptic connections have been shown to exist that are either local (intracolumnar, i.e. largely within a barrel column, range ~150 µm) or long-range (transcolumnar; projecting across several barrel columns). Moreover, synaptic connections can be either intralaminar (within a respective cortical layer) or translaminar (between cortical layers) in nature. Furthermore, the direction of synaptic signalling can be either uni-directional as in cortical relay circuits, or reciprocal, i.e. both neurons in a pair act as pre- and postsynaptic neurons.

Most synaptic connections studied so far in the neocortex and specifically in the barrel cortex are local and intralaminar (for an example, see Fig. 5a). The majority of intralaminar connections exhibit a remarkably high degree of reciprocal, bi-directional coupling (Atzori et al. 2001; Feldmeyer et al. 1999, 2002, 2006; Holmgren et al. 2003; Markram et al. 1997a). This may allow recurrent excitation (and in combination with the feed-forward inhibition recruited by thalamic afferents enhance effective inputs; Miller et al. 2001; Pinto et al. 2003), feedback inhibition or—in case of recurrent connections between two inhibitory neurons—disinhibition. In contrast to intralaminar connections, translaminar connections are apparently characterized by a uni-directional vertical (feed-forward) signal flow (Feldmeyer et al. 2002, 2005; Reyes and Sakmann 1999; Shepherd et al. 2005; Shepherd and Svoboda 2005; Silver et al. 2003; Tarczy-Hornoch et al. 1999). Furthermore, there is a preferential direction of synaptic signalling from the thalamic input layer 4 to supragranular cortical layers and from there back to infragranular layers. In line with this, excitatory L4–L2/3 (Feldmeyer et al. 2002; Shepherd and Svoboda 2005), L2/3–L2/3 (Atzori et al. 2001; Feldmeyer et al. 2006; Holmgren et al. 2003; Fig. 5a) and L2/3–L5B connections (Reyes and Sakmann 1999; Schubert et al. 2001; Shepherd et al. 2003) are dominant while those in the opposite direction are less frequent (Shepherd et al. 2005).

cap. A

Segregated input pathways to the barrel cortex

In the whisker-to-barrel cortex system, sensory information processing is already segregated in the brain stem, giving rise to the so-called lemniscal and paralemniscal pathway, which are relayed through the ventral posteromedial nucleus (VPM) and the posterior medial nucleus (POm), respectively (Ahissar et al. 2000; Diamond 1995; Fig. 2). These two extra-cortical input pathways provide feed-forward excitation to the neocortex, but have distinct projection targets in the barrel column. VPM projection neurons send axons to cortical layers 3, 4, 5B, and 6A of the barrel-related columns, with the highest axonal density in layer 4 (Chmielowska et al. 1989; Koralek et al. 1988; Lu and Lin 1993). Excitatory spiny neurons in layer 4 are densely innervated by these afferents and receive excitatory signals at short latency (Bruno and Sakmann 2006). The thalamocortical EPSPs are, however, rather weak (~1 mV) but synchronously active (Fig. 6). L4 spiny neurons are therefore the dominant element in intracortical signal processing (Ahissar et al. 2000; Bruno and Sakmann 2006; Laaris et al. 2000; Petersen and Sakmann 2001). In vivo recordings from the VPM-L4 spiny neuron connection



cap. A **Fig. 4** Methods to study connectivity in a cortical column. **a** Combination of whole-cell recording of pyramidal neurons in layer 5A and caged glutamate photolysis. Coronal slice of the rat somatosensory cortex with recording electrode positioned in layer 5A and electrical stimulation electrode placed at the *white* matter/layer 6 border. The *white triangle* marks the position of the recorded pyramidal neuron soma in vertical alignment with a layer 4 barrel (*black rounded frames*). At 10 s intervals, up to 450 fields of 50 × 50 µm size (*grid*) were photo-stimulated in sequence covering
cap. B all cortical layers and at least two barrel-related columns. **b** Direct responses and synaptically mediated activity in a layer 5A pyramidal cell, induced by sequential multi-site uncaging of glutamate. Photomicrograph of the native coronal slice and, superimposed, the somatodendritic reconstruction of the recorded neuron as well as the topographic map showing the origins of photolysis induced activity. *Colour code* represents the delay between flash stimulus and the onset of first detected flash related activity in the recorded cell. Activity with delay to onset times < 5 ms is restricted to fields containing dendrites of the recorded neuron and represents direct responses. The *large black frame* illustrates the extent of the investigated cortical
cap. C area; *rounded black frames* mark the barrels in layer 4. **c** Recordings of the membrane potential at V_h = –60 mV obtained after flash stimulation (*yellow arrows*) of fields as indicated by the numbers in **b**. (❶)–(❸) Direct excitatory responses, starting almost immediately after flash stimulation at perisomatic sites and reaching threshold (❶) and followed by flash-induced excitatory postsynaptic potentials (EPSPs, (❸)). (❹), (❺) Flash-induced multiple EPSPs. (❻), (❼) Flash-induced inhibitory postsynaptic potentials (IPSPs); in (❻) the IPSPs shunt the preceding direct response (reprinted from Schubert et al. 2006, Cereb Cortex 16:223–236; with permission from Oxford University Press). **d** *Neurolucida* reconstruction of a layer 4 spiny
cap. D stellate neuron synaptically coupled to layer 5A pyramidal cell. The axonal arborisation of the presynaptic spiny stellate neuron is given in blue, its dendritic configuration in *red*; the axon of the postsynaptic L5A pyramidal cell is *green*, its somatodendritic domain is *white*. **e**,
cap. E *left* Ten consecutive EPSPs recorded in an L5A pyramidal cell elicited by action potentials in a presynaptic spiny stellate cell at an inter-stimulus interval of 15 s. Synaptic efficacy of this connection was relatively low, but failures were not very frequent at this connection. The mean EPSP waveform (*bottom trace*) is shown in *red*. **e**, *right* EPSP amplitude distribution (*red bars*) and baseline noise
cap. E (*white bars*) for this synaptic connection

suggest a high thalamocortical convergence ratio of ~0.43. Given ~200 thalamic cells per VPM barreloid (Land et al. 1995; Varga et al. 2002), a L4 spiny neuron would on average receive ~85 thalamocortical axons (200 neurons ∗0.43 connections/neuron; Bruno and Sakmann 2006). Besides L4 spiny neurons, L3, L5B and L6A pyramidal cells are also targeted by VPM afferents (Bureau et al. 2006) but a detail functional and morpho- detailed

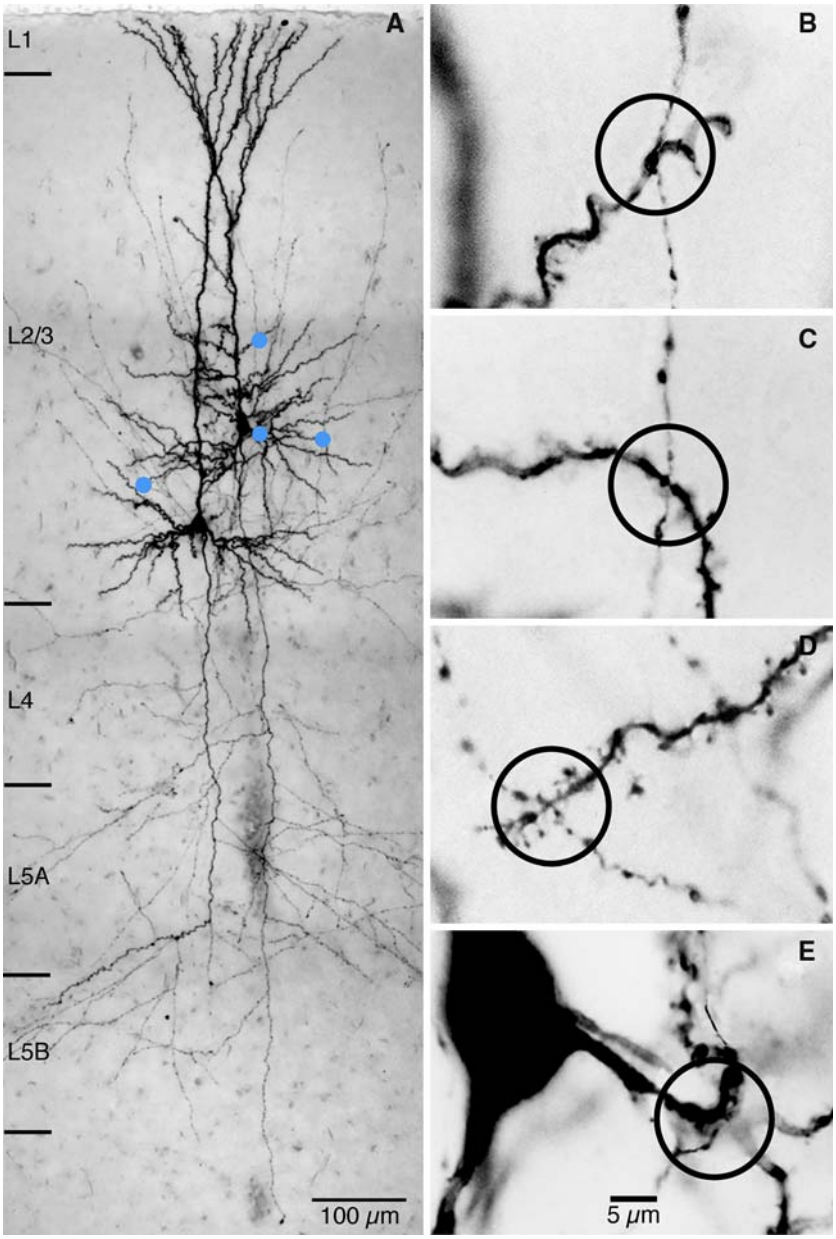


Fig. 5 Pair of synaptically coupled layer 2/3 pyramidal neurons in the rat barrel cortex. cap. A **a** Low power micrograph of a pair of biocytin-labelled layer 2/3 pyramidal neurons. Here synaptic contacts between the presynaptic pyramidal neuron (*left*) and the postsynaptic pyramidal neuron at various dendritic locations are indicated cap. B-E by *blue dots*. **b–e** Individual synaptic contacts (within the *circled areas*) established by the presynaptic *en passant* axon on the postsynaptic dendrite

logical description of these synaptic connections has yet not been performed. In contrast to VPM neurons, POm projection neurons send axons mainly to layers 5A and 1 as well as to the so-called septa between the barrels in layer 4 (Chmielowska et al. 1989; Koralek et al. 1988; Lu and Lin 1993). POm neurons have been shown to innervate predominantly pyramidal cells in layer 5A (Bureau et al. 2006).

The canonical microcircuit

Intralaminar connections between excitatory spiny neurons in layer 4 are the starting point of the so-called 'canonical' signal-processing pathway in the neocortex (first described for the visual cortex by Douglas et al. 1991; reviewed by Douglas and Martin 2004; see also Figs. 7, 8a). In both visual and barrel cortex these connections have been shown to possess a high synaptic efficacy (i.e. a large mean unitary EPSP amplitude: 1.0–1.6 mV) and are very reliable and highly interconnected (Stratford et al. 1996; Feldmeyer et al. 1999; Tarczy-Hornoch et al. 1999; Petersen and Sakmann 2000), at least in young animals. Some of these connections were sufficiently strong to activate postsynaptic action potentials, probably due to the boosting effect of a particularly large NMDA receptor mediated EPSP component (Feldmeyer et al. 1999; see also Nevian and Sakmann 2004). cap. A

L4 spiny neurons display a high degree of recurrent connectivity (rate of reciprocal connections 0.2–0.3; Feld-

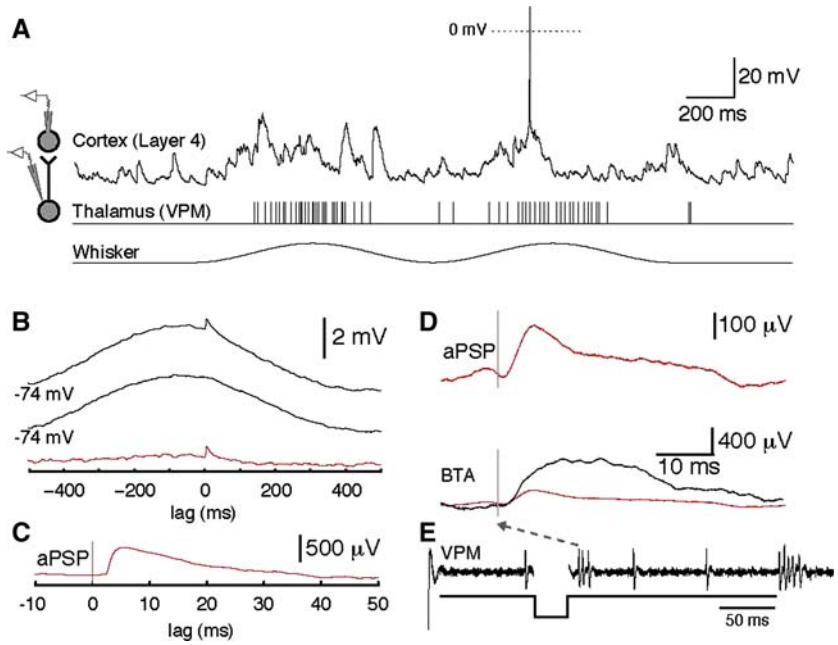


Fig. 6 Unitary EPSPs measured in vivo at a thalamocortical synapse. **a** Simultaneous intracellular recording of a cortical L4 neuron (Cortex) and extracellular recording of a somatotopically aligned thalamic neuron (Thalamus) during whisker stimulation (Whisker). **b** Thalamocortical synapse onto an L4 spiny stellate neuron. *Top* to *bottom*, spike-triggered average, stimulus-induced correlation, difference giving aPSP (thalamic APs, n = 1,526). **c** Expanded view of aPSP. **d** Example of one of the smallest aPSPs observed (thalamic APs, n = 9900). A star pyramidal neuron, 720 µm from the pial surface. **e** Electrical tests (*black*; n bursts = 460) for the same pair that produced the aPSP (*red*) in **d** (reprinted from Bruno and Sakmann 2006, Science 312:1622–1627; with permission from AAAS)

cap. A
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meyer et al. 1999) suggesting that local connections were clustered. Recurrent connections in the neocortex have been proposed to act as feedback amplifiers of synaptic signals within the neocortex (Douglas et al. 1995) although the net effect of this amplification depends on synaptic efficacy, feed-forward and feedback inhibition and the density of synaptic connections (Chance et al. 1998). Whether feedback amplification does indeed occur given the high degree of convergence of the thalamocortical afferents and the presence of feed-forward inhibition in the barrel cortex a matter of debate (Pinto et al. 2003; Bruno and Sakmann 2006).

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Morphologically, L4 spiny neurons in the barrel cortex are characterized by mainly vertically oriented, predominantly intracolumnar axons that target preferentially L2/3 pyramidal cells, independent of whether they are located in the upper and lower part of this layer (Feldmeyer et al. 2002; Lübke et al. 2000, 2003; Shepherd and Svoboda 2005; Silver et al. 2003). For mouse barrel cortex, on the other hand, a predominant innervation of pyramidal neurons in 'layer 3' has been reported (Bureau et al. 2006). The translaminar signal flow between layer 4 and 2/3 is uni-directional and mainly confined to a cortical column (Fig. 7). The connectivity between spiny L4 neurons and L2/3 pyramidal cells is remarkably high (~0.1) despite the large distance between the pre- and postsynaptic neurons. L4–L2/3 connections have a comparatively low synaptic efficacy (mean unitary EPSP amplitude: 0.7 mV; Feldmeyer et al. 2002) but at low frequency stimulation show a high reliability (presynaptic release probability: 0.8; Silver et al. 2003). Signal transmission to L2/3 pyramidal cells is therefore likely to have a high threshold requiring the simultaneous activation of about 50 spiny L4 neurons. This implies that this synaptic connection may function as a 'gate' for the lateral spread of excitation within layer 2/3.

In contrast to the columnar organization of the L4 axons, L2/3 pyramidal cell axons have two distinct domains: one vertical, confined to the column and one horizontal with long-range (2–4 mm) projecting axonal collaterals. In layer 2/3 the excitatory signal flow in the neocortex can take either an intracolumnar or a transcolumnar route (Fig. 7). The main target structures of L2/3 pyramidal cells are other pyramidal cells in layer 2/3 (Egger et al. 1999; Feldmeyer et al. 2006; Holmgren et al. 2003) and 5B (Atzori et al. 2001; Reyes and Sakmann 1999; Thomson and Bannister 1998). For pairs of L2/3 pyramidal cells only local, intracolumnar connections (i.e. within a range of 100 µm) have been studied in detail. Excitatory signal flow within layer 2/3 can be either uni- or bi-directional (Atzori et al. 2001; Feldmeyer et al. 2006; Holmgren et al. 2003). The connectivity of L2/3 pyramidal cells is high for local connections (probability of ~0.1; Feldmeyer et al. 2006; Holmgren et al. 2003) but decreases dramatically (0.01) for larger intersomal distances (>200 µm; Holmgren et al.

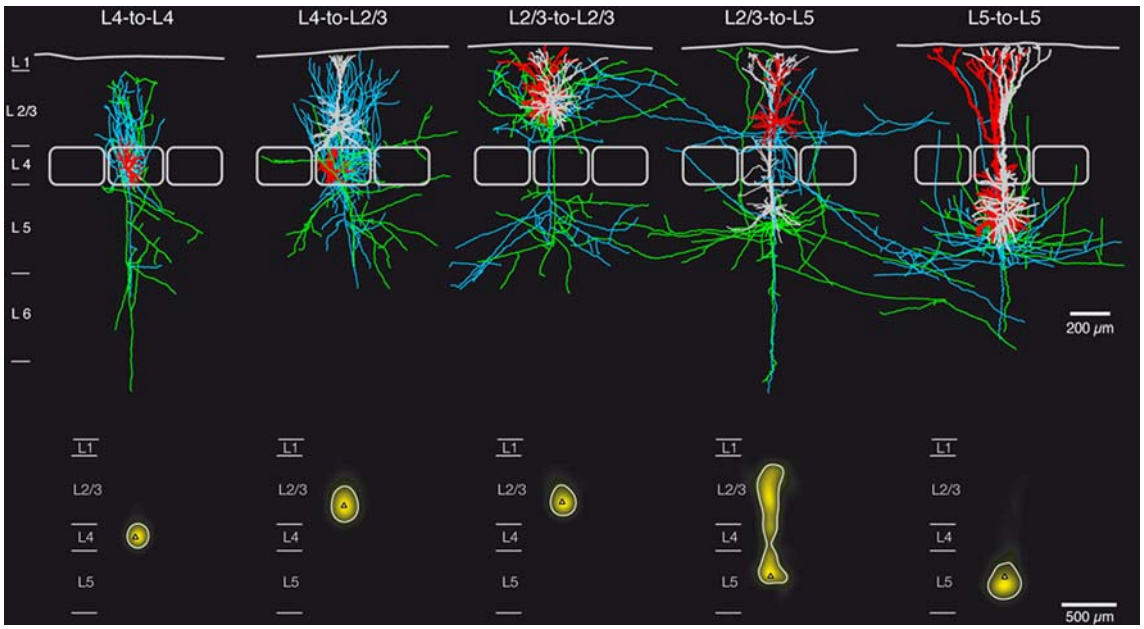

Fig. 7 Canonical microcircuit of the different excitatory synaptic connections in barrel field of the somatosensory cortex. Excitatory synaptic connections involved in intracortical signal processing (presynaptic neurons: somata and dendrites *red*, axons *blue*; postsynaptic neurons: somata and dendrites *white*, axons *green*). *Top row*, from *left to right*: pair of layer 4 spiny stellate cells; layer 4 spiny stellate—layer 2/3 pyramidal cell pair, pair of layer 2/3 pyramidal cells; layer 2/3 pyramidal cell—layer 5 pyramidal cell pair; layer 5 pyramidal cells pair. *Bottom row*, corresponding synaptic innervation domains (centred on the postsynaptic somata, *open triangles*) obtained from the product of the presynaptic axonal densities and the postsynaptic dendritic densities

2003). The synaptic efficacy is comparatively low (mean unitary EPSP amplitude 0.3–1.0 mV; Atzori et al. 2001; Feldmeyer et al. 2006; Holmgren et al. 2003). Interestingly, the release probability and the response to repetitive stimulation in these connections differ substantially between sensory cortices. While in auditory cortex two distinct subpopulations with a low (0.13) and a high release probability (0.68), were found (Atzori et al. 2001), only connections with a very high release probability (0.93) were observed in barrel cortex (Feldmeyer et al. 2006; Holmgren et al. 2003). There are several implications of these findings. L2/3 pyramidal cell connections are not homogeneous both within and between sensory cortices. Thus, signal processing by these connections is diverse in different sensory cortices and may be adapted to the type of sensory input. For example, in auditory cortex the two classes of connections may provide a substrate of differential signal processing of transient vs. sustained stimuli (Atzori et al. 2001). In addition, pyramidal cells in layer 2/3 are not a homogeneous population of neurons but fall into groups with different morphological and functional properties (Brecht et al. 2003; Bureau et al. 2006; Feldmeyer et al. 2006; Lübke et al. 2003). In summary, connections between pyramidal cells in layer 2/3 may integrate and subsequently distribute excitatory signals arriving from layer 4 across laminar and columnar borders (Fig. 7). Local connections between pyramidal cells in layer 2/3 could also help to synchronize the activity of neuronal ensembles with similar functional properties even over a wide range of cortical surface, i.e. over different cortical columns.

The other main targets of L2/3 pyramidal cells are L5B pyramidal cells possessing an apical dendrite terminating in a thick wide-range tuft (Reyes and Sakmann 1999; Schubert et al. 2001; Thomson and Bannister 1998). These pyramidal cells constitute one class of 'output' neurons of the neocortex with axonal projections to various subcortical brain regions. The reported mean unitary EPSP amplitudes differ substantially (range 0.1–0.8 mV), but the majority of connections appears to have a relatively low synaptic efficacy, in particular in more mature animals indicating that the synaptic efficacy is developmentally regulated (Reyes and Sakmann 1999). The function of the connection between L2/3 and L5 pyramidal cells is difficult to assess but it may serve as an intracolumnar relay and act as an integrator of cortical signals arriving at the presynaptic neuron both from intra- and transcolumnar neuronal ensembles.

Excitatory synaptic connections between neighbouring 'thick-tufted' L5B pyramidal cells projecting to subcortical areas such as pontine nuclei, tectum, thalamus brainstem and spinal cord have been studied extensively (Fuhrmann et al. 2002; Kozloski et al. 2001; Le Bé and Markram 2006; Le Bé et al. 2006; Markram and Tsodyks 1996; Markram et al. 1997a, b, 1998; Ohana and Sakmann 1998; Song et al.

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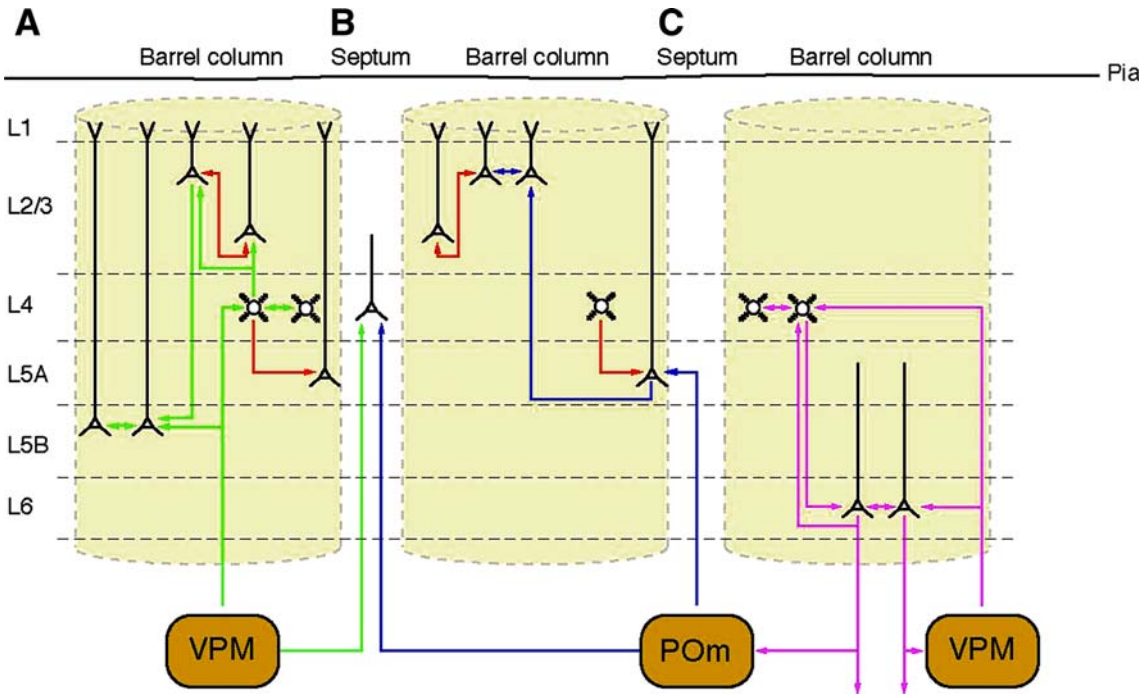

Fig. 8 Simplified scheme of parallel cortical microcircuits in the barrel cortex. **a** The 'canonical' microcircuits receiving lemniscal thalamic input from the ventroposterior medial nucleus (*VPM*) predominantly in layer 4 (and to lesser degree in layer 5B); see text for details. **b** Intracortical microcircuits involved in the processing from signals arriving from the paralemniscal pathway (input from the posterior medial thalamic nucleus, POm, to L5A pyramidal neurons). **c** Synaptic connections involved in the thalamo-cortical-cortico-thalamic feedback circuit between layer L4 spiny neurons, L6 pyramidal cells and the VPM. Note that barrel L4 spiny neurons are intrinsic elements of all three microcircuits and that septal L4 neurons receive both VPM and POm input (see text for details). The intracortical connectivity of septal neurons has been omitted for simplicity. *Colour code*: *Green* 'canonical' microcircuit, *blue* 'paralemniscal' pathway, *red* intracortical microcircuits interdigitating 'lemniscal' and 'paralemniscal' microcircuits, *violet* thalamo-cortical-cortico-thalamic loop

cap. A

cap. B

cap. C

2005; Tsodyks and Markram 1997). These neurons show a high connectivity with each other as was also revealed by photostimulation (Schubert et al. 2001) and synaptic connections form cluster-like arrangements. At low frequency stimulation, the synaptic efficacy of L5B–L5B pyramidal cell connections is high (mean unitary EPSP amplitude 1.2–1.3 mV). Synaptic transmission exhibits a higher CV (0.52) and failure rate (14%) than observed for L4–L4 (5%) and L4–L2/3 connections (2%), indicating a somewhat lower reliability. It has been postulated that ensembles of interconnected L5B pyramidal cells contribute to synchronized electrical activity via their long-range horizontal axonal collaterals. Synchronized excitatory input to these ensembles may arrive from the cortico-cortical association fibres establishing synapses with pyramidal cells at their apical tufts. This concerted activity is not only distributed horizontally within the cortex but also to subcortical structures.

Recently, synaptic connections of a subpopulation of so-called untufted L5B pyramidal cells that project via the corpus callosum have been described in neonatal rat neocortex (Le Bé et al. 2006). The connectivity between these pyramidal cells is lower than that for thick-tufted neurons and their unitary EPSP amplitude (0.8 mV) and release probability is lower while other properties are rather similar. It has been suggested that these neurons possess a lower integrative capacity than the highly interconnected network of thick-tufted pyramidal cells.

A paralemniscal microcircuit in the neocortex?

As already mentioned above, two segregated inputs into the barrel cortex exist: the lemniscal and paralemniscal pathways. While the lemniscal pathway leads to the 'canonical' circuits diagram describe above, the paralemniscal pathway takes a different route, innervating predominantly layer 5A. Here, the major target neurons are L5A pyramidal cells that possess slender apical dendrites with small tufts (Manns et al. 2004; see Fig. 8b). In contrast to cortical neurons with lemniscal thalamic input that have short stimulus-response latencies, the activation of L5A pyramidal cells has longer latencies (Ahissar et al. 2000; Armstrong-James et al. 1992). These neurons target mainly pyramidal cells in the upper part of layer 2/3 (layer 2), in particular those above the barrel septa (Shepherd and Svoboda 2005). Therefore, it has been suggested that a functionally distinct

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'layer 2' exists in the rodent neocortex. L2/3 pyramidal cells receive a largely columnar input from L4 spiny neurons (Feldmeyer et al. 1999; Laaris et al. 2000; Lübke et al. 2003; Petersen and Sakmann 2001; Shepherd and Svoboda 2005), while 'L2' pyramidal cells receive a multicolumnar input from layer 5A (at least in mouse barrel cortex; Bureau et al. 2006).

It has been hypothesized that the two distinct input pathways are preserved in the barrel cortex (Ahissar et al. 2000; Brecht et al. 2003; Bureau et al. 2006) and that the activity of POm neurons primarily encodes information about whisking, while VPM neurons encode combined information about whisking and whisker-object contact (Yu et al. 2006). The lemniscal and paralemniscal pathways are proposed to converge in 'layer 2' (Bureau et al. 2006).

A number of findings make such separate pathways rather unlikely. Firstly, septal L4 spiny neurons, the somata and proximal dendrites of which are located in a region innervated by POm (Chmielowska et al. 1989; Koralek et al. 1988; Lu and Lin 1993), extend their distal dendrites into the barrels, which are innervated by VPM (Simons and Woolsey 1984). Indeed, functional monosynaptic connections between VPM and septal neurons have been demonstrated (Bruno and Simons 2002; Bruno and Sakmann 2006). Secondly, a synaptic connection between L4 spiny neurons and layer 5A pyramidal cells exist in rat barrel cortex (Feld-
cap. B-D meyer et al. 2005; Schubert et al. 2006; see Fig. 4b–d) which may account for the narrow receptive fields of these neurons (Manns et al. 2004). Intralaminar connections between L5A pyramidal cells exist as well (Frick et al. 2007). Furthermore, pyramidal cells in lower and upper layer 2/3 receive input from L4 spiny neurons (Feldmeyer et al. 2002). This connection is of high reliability but relatively low efficacy (mean unitary EPSP amplitude 0.6 mV). All these synaptic connections represent early points of convergence for both thalamic input pathways and therefore challenges the idea of entirely segregated microcircuits in the barrel cortex with a single convergence in 'layer 2'. Rather, it argues for strongly interdigitated neuronal networks at multiple levels that balance and synchronize incoming sensory information (cf. Fig. 8).

Cortico-thalamic feedback loop

Cortico-thalamic projections are about tenfold more numerous than thalamocortical projections (Guillery 1967; Liu et al. 1995) but their function is still barely understood. Because layer 6 of the cerebral cortex receives direct thalamic input and provides projections back to the thalamus, it is in a unique position to influence thalamocortical signal
cap. C flow (Fig. 8c).

Electron microscopic studies of HRP labelled axon terminals in layer 4 of the visual cortex in vivo demonstrated the existence of a weak synaptic connection with L4 spiny neurons (McGuire et al. 1984; Ahmed et al. 1994). Paired recordings have revealed the existence of a functional L6 pyramidal cell-to-L4 spiny neuron connection in young adult cat visual cortex (Tarczy-Hornoch et al. 1999). This synaptic connection has a low efficacy (mean EPSP amplitude 0.2 mV), a high CV (0.72), relatively low release probability (0.37–0.56) and exhibits a frequency-dependent facilitation of the EPSP amplitude. This implies that with time the synaptic input from layer 6 to layer 4 may increase during sustained stimulation. It may therefore compensate for the decrease in the synaptic response at the connection between pairs of L4 spiny neurons (exhibiting frequency-dependent depression).

An excitatory feedback loop from layer 4 to layer 6 exist as well, but has only been confirmed in a single paired recording (Tarczy-Hornoch et al. 1999). Similarly, photostimulation showed weak inputs from superficial layers to L6 pyramidal cells (Zarrinpar and Callaway 2006), contrasting sharply with L6 neurons in the primate visual cortex (Briggs and Callaway 2001).

Within layer 6, two major subtypes of pyramidal neurons exist with respect to their structural and functional properties (Mercer et al. 2005; Zarrinpar and Callaway 2006; Zhang and Deschenês 1998): cortico-cortical projecting (i.e. with long horizontal intracortical axons confined to infragranular layers) and cortico-thalamic projecting (i.e. those projecting to different thalamic nuclei) pyramidal cells. 'Cortico-cortical' L6 pyramidal cells were 2–4 times more likely to innervate other L6 pyramidal cells than were cortico-thalamic L6 pyramidal cells but less likely to innervate inhibitory interneurons (Mercer et al. 2005). The functional properties of pairs of cortico-cortical pyramidal cells and those between cortico-cortical and cortico-thalamic neurons are also different. While connections between cortico-cortical neurons were of low reliability (CV 0.6) and had mean EPSP amplitudes of 0.9 mV, connections between a presynaptic cortico-cortical and a postsynaptic cortico-thalamic L6 pyramidal cell were more reliable (CV 0.2) and had significantly larger mean unitary EPSP amplitudes (1.7 mV); both types of L6 connections exhibited paired pulse depression. Besides forming intralaminar connections, cortico-cortical L6 pyramidal cells were found to target also L5B pyramidal cells (Mercer et al. 2005). Thus, the ensemble of pyramidal cells in layer 6 is part of an intricate network linking cortical input layers back to different thalamic nuclei. For the barrel cortex, it has been shown (Temereanca and Simons 2004) that cortico-thalamic feedback connections from layer 6 neurons help to sharpen the spatial response properties of thalamic neurons in VPM by recruiting topographically specific excitatory and inhibitory mechanisms. Such a mechanism may also be at work for other sensory cortices

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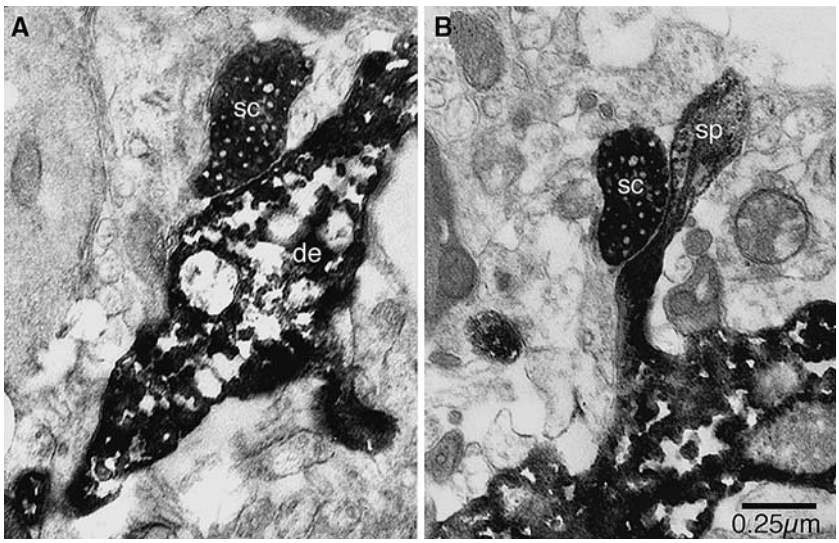

Fig. 9 Target specificity of synaptic contacts. **a** Synaptic contacts (*sc*) established by the presynaptic *en passant* axon on the dendritic shaft (*de*) of a postsynaptic layer 2/3 pyramidal neuron. **b** Synaptic contact (*sc*) established by the presynaptic *en passant* axon on a dendritic spine (*sp*) of a postsynaptic dendrite (*de*) of a layer 2/3 pyramidal neuron

(Sillito and Jones 2002). However, the properties of the individual cortico-thalamic connections involved in these processes have so far not been elucidated.

Cortico-thalamic axonal projections originate also from neurons in layer 5 (in particular layer 5B; Bourassa et al. 1995) but while L5B pyramidal cells receive synaptic input from VPM their thalamic target region is the dorsal part of the posterior group, where they form clusters of giant terminal boutons, which may be involved in enhancing spatio-temporal discrimination (Hoogland et al. 1991; Veinante et al. 2000; Wright et al. 2000).

Synaptic innervation domains of excitatory connections

There is growing evidence that synaptic contacts between excitatory neurons in a cortical column are also target-specific as has been described for cortical GABAergic interneurons (Somogyi et al. 1982; Tamás et al. 1998, 2000, 2003; for a review see Soltesz 2006). Characteristic for excitatory connections is the exclusive innervation of

cap. A B

dendritic shafts (Fig. 9a) or spines (Fig. 9b) on the post-synaptic neuron. Synaptic contacts are mainly found on basal dendrites (63–85% for L5A–L5A, L5B–L5B, L4–L4, L4–L2/3, L4–L5A, L2/3–L2/3 cell connections, Feldmeyer et al. 1999, 2002, 2005, 2006; Frick et al. 2007; Lübke et al. 2000, 2003; Markram et al. 1997a, b; Le Bé et al. 2006; Figs. 5d–e, 9). Only a small fraction (less than 10%) was located on apical oblique or terminal tuft dendrites. The majority of synaptic contacts were located relatively close to the soma (L4–L4: 69 μm; L4–L2/3: 67 μm; L2/3–L2/3: 91 μm; L5A–L5A: 107 μm; L5B–L5B: 147 μm). Synaptic contacts in the apical tuft have only been found for pyramidal cells in layer 5 (Feldmeyer et al. 2005; Markram et al. 1997a). The number of synaptic contacts varied from 2 to 8 between individual connections but a strong correlation between the number of synaptic contacts and size of the EPSP amplitude was not found for individual connections. However, the relatively short geometric distance of synaptic contacts implies a short electrotonic distance and hence effective transmission from dendrite to soma. Apart from specificity with respect to subcellular target region, there is also growing evidence that the axons of excitatory neurons display target neuron specificity (Beierlein et al. 2003; Koester and Johnston 2005; Kozloski et al. 2001; Markram et al. 1998; Reyes et al. 1998) as earlier described for interneurons in neocortex and hippocampus (reviewed by Freund and Buzsáki 1996; Somogyi et al. 1998; Markram et al. 2004; Soltesz 2006). This strongly suggests that cortical connectivity is far from being random as has long been assumed (Braitenberg and Schüz 1991; Hellwig 2000; Hellwig et al. 1994).

Synaptic dynamics of excitatory neocortical connections

Cortical neurons transmit information by responding selectively to changes in the spatial and temporal pattern of presynaptic action potentials arriving at about 10,000–15,000 synapses per neuron. The amplitude of the postsynaptic response is dynamically adjusted by the presynaptic activation pattern. Most excitatory connections in the neocortex show synaptic depression following repetitive stimulation (Feldmeyer et al. 2002, 2005, 2006; Frick et al. 2007; Markram et al. 1997a, b, 1998; Tsodyks and Markram 1997; Petersen 2002; Reyes and Sakmann 1999). The frequency-dependent behaviour of a synapse (it's 'short-term plasticity') is largely target neuron specific (Reyes and Sakmann 1999; Galaretta and Hestrin 1998; Markram et al. 1998; Reyes et al. 1998; Varela et al. 1999;

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Gupta et al. 2000), region-specific (Atzori et al. 2001), appears to be developmentally regulated (Angulo et al. 1999; Bolshakov and Siegelbaum 1995; Pouzat and Hestrin 1997; Reyes and Sakmann 1999) and exhibits a high variability for a specific type of connection (Tsodyks and Markram 1997). The short-term dynamics of intra- and transcolumnar synaptic connections in the barrel cortex may be altered by sensory deprivation (Finnerty et al. 1999). Alterations of the transcolumnar pathways amplified changes in the vertical inputs and may thereby help to induce a functional reorganization of cortical columns.

The strength or 'information content' of a certain type of synaptic connection is maximal at a particular activation frequency unique to that synapse. Depressing neocortical synapses are adapted for coding temporal information at low action potential firing rates, as reported for spontaneous firing of cortical neurons; the may carry significant information about the timing of up to four preceding presynaptic spikes. In contrast, it has been suggested that facilitating synapses are optimized to operate at higher presynaptic rates (9–70 Hz) more reminiscent to the evoked activity in excitatory neocortical neurons and may represent the timing of over eight presynaptic spikes (Fuhrmann et al. 2002). It remains to be determined, however, whether in the *awake animal* the frequency of spontaneous and evoked activity at *individual* synaptic connections is indeed as high as has been suggested in this publication. More recently, 'sparse' action potential coding of incoming sensory information (i.e. coding with low action potential firing rates) has been shown in some regions of the neocortex among which is the barrel cortex (Brecht et al. 2003; Brecht and Sakmann 2002; de Kock et al. 2007; Kerr et al. 2005; for a review see Shoham et al. 2006).

Summary

Studies on synaptically coupled cortical neurons have steadily increased our knowledge about structural and functional properties of individual connections. It is now established that excitatory synaptic connectivity is not random but cell- and region-specific. Most excitatory connections exhibit a remarkable high reliability at low stimulus frequencies but vary to a large extent in both synaptic efficacy and their dynamic properties. This suggests that the different microcircuits are precisely tuned with respect to the sensory signal transformation in the columnar network. To understand the cortical column and its function as a unit much more information is required about individual synaptic microcircuits, their interaction and modulation within the framework of the cortical column. Only then will we be able to construct a biologically relevant input–output relationship for sensory signalling in the neocortex. However, this requires a combination of different experimental approaches. Paired or multiple recordings in acute brain slices will be one of them, particularly when combined with imaging techniques revealing intracellular calcium dynamics. Photostimulation using caged glutamate or optical probing techniques will help to identify the large-scale connectivity of neuronal networks, i.e. to unravel transcolumnar networks. To investigate cortical signal flow in neuronal ensembles, intrinsic or voltage sensitive dye imaging are invaluable. Furthermore, data obtained from acute slices have to be compared with the in vivo situation, preferentially in the sedated or even the *awake* animal. Where possible, paired recordings will proof to be invaluable. Finally, network models using realistic microcircuits will enable us to understand the computational properties of a cortical column. The combination of these techniques may help to unravel the dynamics of neuronal signalling within and between cortical columns.

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