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REVIEW

Mapping functional connectivity in barrel-related columns reveals layer- and cell type-specific microcircuits

Dirk Schubert · Rolf Kötter · Jochen F. Staiger

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Abstract Synaptic circuits bind together functional modules of the neocortex. We aim to clarify in a rodent model how intra- and transcolumnar microcircuits in the barrel cortex are laid out to segregate and also integrate sensory information. The primary somatosensory (barrel) cortex of rodents is the ideal model system to study these issues because there, the tactile information derived from the large facial whiskers on the snout is mapped onto so called barrel-related columns which altogether form an isomorphic map of the sensory periphery. This allows to functionally interpret the synaptic microcircuits we have been analyzing in barrel-related columns by means of whole-cell recordings, biocytin filling and mapping of intracortical functional connectivity with sublaminar specificity by computer-controlled flash-release of glutamate. We find that excitatory spiny neurons (spiny stellate, star pyramidal, and pyramidal cells) show a layer-specific connectivity pattern on top of which further cell type-specific circuits can be distinguished. The main features are: (a) strong intralaminar, intracolumnar connections are established by all types of excitatory neurons with both, excitatory and (except for layer Vb- intrinsically burst-spiking-pyramidal cells) inhibitory cells; (b) effective translaminar, intracolumnar connections become more abundant along the three main layer compartments of the canonical microcircuit, and (c) extensive transcolumnar connectivity is preferentially found in specific cell types in each of the layer compartments of a barrel-related column. These multiple sequential and parallel circuits are likely to be suitable for specific cortical processing of ''what'' ''where'' and ''when'' aspects of tactile information acquired by the whiskers on the snout.

Keywords Barrel cortex · Columnar modules · Microcircuits · Excitatory spiny neurons · Caged glutamate

D. Schubert (✉) · R. Kötter
Department of Cognitive Neuroscience,
Radboud University Nijmegen Medical Centre,
POB 9101, 6500 HB Nijmegen, The Netherlands
e-mail: d.schubert@cns.umcn.nl

R. Kötter
Institute of Anatomy 2 and
C. & O. Vogt-Institute for Brain Research,
Heinrich-Heine-University Düsseldorf,
POB 101007, 40001 Düsseldorf, Germany

J. F. Staiger
Department of Neuroanatomy,
Institute of Anatomy and Cell Biology,
Albert-Ludwigs-University Freiburg,
POB 111, 79001 Freiburg, Germany

Introduction

The cerebral cortex, especially that of mammals, is the part of the brain which is crucial for ''higher'' cognitive performance, such as, (a) the analysis and conscious perception of sensory stimuli, (b) the planning and regulation of goal-directed movements as well as (c) learning and memory. The structural basis of the underlying functional processes are interconnected modules: unique cortical areas and, at a submillimeter scale, the rather stereotypical cortical column, which is particularly evident in sensory cortices. Because of the enormous complexity of cortical architecture a focused approach investigating cortical signal processing within and among cortical columns seems to provide a useful first step in the analysis of structure-function relationships of the cerebrum.

The cortex: areas, layers, and columns

The rat cortex shows a high degree of areal and laminar differentiation (Zilles and Wree 1995). There are various functional and structural parameters indicating that rodents—in spite of their lissencephalic brain—are a suitable object for the experimental exploration of morphological and physiological principles that may be generalized to the brains of other mammals, including humans. Especially the primary sensory cortical areas offer a good inter-species comparability with respect to their basic organization. Principles that are valid for all mammals are: (a) the distinct laminar arrangement of the primary cortical areas in basically six different layers—parallel to the pial surface—(see Fig. 1c, here somatosensory or barrel cortex) as well as (b) the representation of sensory surfaces in the form of topological maps (see Fig. 1a, b; Welker 1971; Welker and Woolsey 1974). The basic principle of such a topological map is that it preserves neighbor relationships of peripheral receptors in the central nervous system even though the relative sizes of the represented receptive fields may differ depending on peripheral receptor densities and behavioral significance of these. A ''labeled-line'' of sequentially connected neurons ensures that the central-nervous representation of adjacent receptive surfaces in the periphery is also maintained in all subcortical processing and synaptic relay stations and the cortex, at least in primary sensory areas (Waite 2004). In the sensory cortices those ''labeled-line'' projections preferentially end in the *lamina granularis* (IV). In the primary somatosensory cortex of rodents layer IV contains periodic cell aggregates which are called *barrels*, because of their anatomical appearance (Jensen and Killackey 1987; Lu and Lin 1993; Staiger et al. 1996).

The homology of the arrangement of the peripheral receptors (associated with the vibrissae or whiskers) and

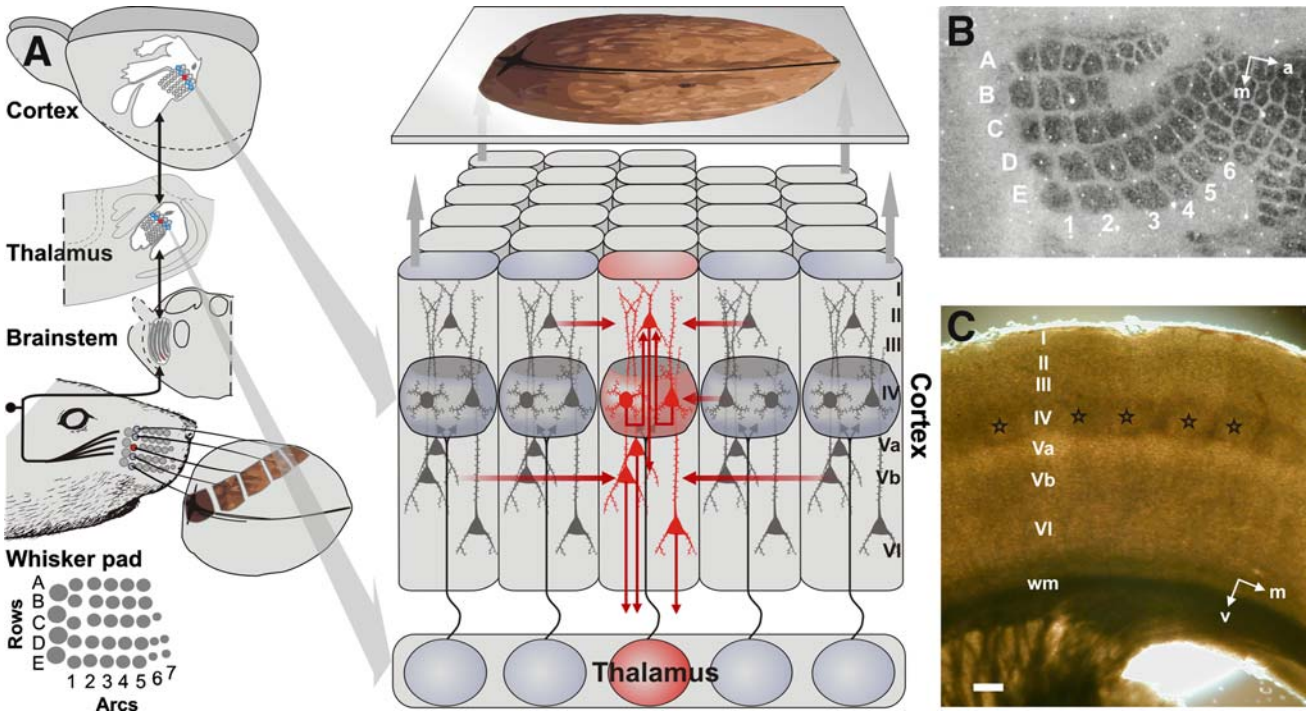

Fig. 1 Hypothetical function of the whisker-to-barrel pathway which forms a major part of the trigeminal somatosensory system. **a** On the snout, the whisker follicles are indicated by *gray circles*, except for whisker C1 which is in red as in all its central representations. Arc 1 whiskers are drawn as *black lines* touching an object. At each level of the pathway an isomorphic arrangement of neuronal cell groups, reflecting the layout of the whiskers on the snout, can be found. These are called *barrelettes* in the primary trigeminal nucleus of the brainstem, *barreloids* in the ventrobasal thalamic nucleus and most prominent *barrels* in the primary somatosensory (*barrel*) cortex. Included into this scheme is our hypothesis that segregating and integrating cortical circuits (shown as *arrows* in the cortex) are contained in this pathway which are capable to perform object identification (here: walnut). **b** Cytochrome oxidase staining of a tangential section through layer IV of the primary somatosensory cortex shows the regular appearance of intensely stained barrels separated by lightly stained septa. Barrels are labeled according to standard nomenclature (Photo provided by courtesy of Pete Land). **c** Acute coronal slice through the barrel cortex of a P19 rat illuminated by Dodt gradient contrast. The barrels in layer IV as such but not their specific whisker identity are clearly identifiable (*asterisks*) as well as all the cortical layers (Roman numerals) that are in vertical register forming a barrel-related column. Scale bar 200 μm; *a* anterior, *m* medial, *v* ventral

the arrangement of the respective barrels (Fig. 1) has soon led to the hypothesis that each barrel is responsible for processing the tactile information that originates from the corresponding contralateral whisker (Woolsey and van der Loos 1970; Welker 1971). This hypothesis has been corroborated several times, even if the concept has been modified in so far that processing the information from a respective whisker is not exclusively but predominantly confined to one barrel (Simons 1978; Ito 1985; Armstrong-James and Fox 1987). Furthermore, each barrel in lamina IV represents the morphological correlate of a functionally related group of neurons that is vertically arranged across the borders of layers, the so-called cortical column. How can such a column be defined? The column is regarded as a functional base unit as demonstrated by physiological techniques showing the similar functional response characteristics of the neurons within one column (Mountcastle 1997). Cortical columns were first established by means of in vivo electrophysiological methods: in the somatosensory as well as in the visual cortex of cats, in a clearly restricted volume spanning across cortical layers, the neurons reacted predominantly or exclusively to adequate sensory stimuli of the same modal and spatial specificity (Mountcastle 1957; Hubel and Wiesel 1962). Recently it was especially the modular organization of the prefrontal cortex with its involvement in working-memory skills that has received considerable attention (Goldman-Rakic 1996). Interestingly, only in the *barrel* cortex a morphological correlate is readily detectable (cf. Agmon and Connors 1991; Schubert et al. 2001; Petersen 2003). Nevertheless, the clear structural demonstration of specific columns necessitated specific stimulation paradigms that we have recently developed (Staiger 2006; Staiger et al. 2000a).

Cellular components of the column: excitatory and inhibitory neurons

Leaving aside glial cells, a column consists of two basically different types of neurons: (a) excitatory principal neurons and (b) inhibitory interneurons (Peters and Jones 1984). The excitatory principal neurons use L-glutamate as the major neurotransmitter and are usually projection neurons, which possess (in addition to local recurrent collaterals) a main axon leaving their home column, in most cases also their respective area. They are also called principal neurons because of their quantitative dominance (see below). The inhibitory interneurons, by contrast, use gamma-aminobutyric acid (GABA) as their neurotransmitter and their axon collaterals predominantly stay within the column, in some cases even within one or only few layers of the column. Therefore, inhibitory interneurons are also called non-principal or *''local-circuit''* cells (Fairen et al. 1984). Cell counts have shown that depending on the cortical area about 75–85% are principal neurons and 12–25% of neurons are GABAergic interneurons (Ren et al. 1992; Beaulieu 1993). Since in this review inhibitory interneurons are not dealt with in greater detail some brief remarks about this cell type should suffice: Depending on the sensitivity or specificity of methods and preferences of the authors up to 20 different types of interneurons have been distinguished which basically fulfill two tasks (Parra et al. 1998; Markram et al. 2004): (a) perisomatic inhibition, which controls the firing pattern of the target cell (mostly so-called basket and chandelier cells) or (b) dendritic inhibition, which controls the integration conditions in the dendritic tree (e.g., Martinotti-cells). In our results that we are going to describe below, these inhibitory cells contributed the layer-specific pattern of inhibitory postsynaptic potentials that we obtained for the excitatory neuron subgroups.

Our studies were concerned with the structural and functional connectivity of excitatory neurons in the primary somatosensory cortex of the rat. Therefore, these cells will be further introduced here. A characteristic of the sensory cortical areas is a prominent *lamina granularis*. This layer IV has been named after its appearance in Nissl stainings which showed densely packed and seemingly sparsely arborized cells that appear ''grain-like,'' i.e., granular. However, later on with the help of Golgi-impregnations a richly arborized and stellate-like character of their spine-laden dendrites could be revealed. Thus, these cells are now called spiny stellate cells (Simons and Woolsey 1984; Lund 1984). Spiny stellate cells are the only excitatory neurons whose axon collaterals primarily remain within one column, which makes them resemble interneurons (Feldmeyer et al. 1999; Staiger et al. 2004). The remaining excitatory neurons of the cortex exhibit rather uniform somatodendritic morphology, which gave rise to the term pyramidal cells. It has been proven that these projection neurons in the supragranular layers (II and III) predominantly issue commissural and associative axonal projections, which differs from those in the infragranular layers (Va, Vb, and VI). There, in addition to associative connections, the pyramidal cells of lamina Va and Vb mostly innervate non-thalamic subcortical target areas *(striatum, colliculus superior, nuclei pontis, etc.)*; the pyramidal cells of lamina VI, however, project almost exclusively to the thalamus (Jones 1981). Moreover, it is now known that at least two electrophysiologically distinct classes of excitatory neurons are existent. According to the action potential firing patterns upon depolarizing current injection during single-cell recordings regular-spiking (RS) and intrinsically burst-spiking (IB) cells can be distinguished (McCormick et al. 1985).

Receptive fields and tactile information processing

It has been shown that excitatory neurons synaptically interact within one layer as well as across layers and columns (cf. Chagnac-Amitai and Connors 1989; Laaris et al. 2000; Petersen et al. 2003b). It is assumed that these interactions have important functional consequences; however, concise experimental evidence is still sparse. Intracolumnar information processing probably deals mainly with the physical parameters of the mechanical stimulation of the whisker that corresponds to the barrel-related column (Simons 1978). That is how the various parameters (e.g., texture, form, size) of the detected objects, but also the position in space of the touched whisker could be extracted as precisely as possible (Kleinfeld et al. 2006). But since presumably no object of the outer world can be coded by one single whisker alone (Hutson and Masterton 1986), an exchange of all sensory information that is transmitted by the entire set of vibrissae that touched an object in space and time must be realized by neuronal circuitry, most probably in the cortex (e.g., the coding of a walnut in Fig. 1a; see also Derdikman et al. 2006). The extent to which a neuron can be directly involved in such an exchange of partial information is described by the size of its receptive field. This is the part of the peripheral sensory surface whose information is transferred to a certain neuron. Neurons within the different cortical layers exhibit distinctively different sizes of their receptive fields. The mechanism and exact consequences of the phenomenon of varying size of receptive fields across cortical layers have not yet been resolved. It can nonetheless be assumed that the larger the receptive field is, the more tactile information is integrated (Simons 1995; Armstrong-James 1995). Thus, layer IV neurons, which are known to exhibit the smallest receptive fields, are basically limited to processing information that originates from the associated whisker. On the contrary, the supragranular layers exhibit more trans-columnar interactions (Petersen et al. 2003a; Feldmeyer et al. 2006), which could be the substrate for the larger receptive field sizes of the neurons found there. Finally, the pyramidal cells of the infragranular layers exhibit the largest receptive fields, which means that they can integrate various pieces of information from distant whiskers (Ito 1985; Simons and Carvell 1989; Moore and Nelson 1998). Possible structural correlates of the latter are (a) the extensive apical dendrite (Larkman and Mason 1990; Larkum et al. 1999; Schubert et al. 2001) as a correlate of massive afferent inputs and (b) the most extensive intracortical axonal arborization as a correlate of most extensive output of all cortical neurons (Gabbott et al. 1987; Gottlieb and Keller 1997; Staiger et al. 1999).

We therefore hypothesize that in each columnar module circuits must exist which (a) ensure processing of the physical characteristics of tactile stimuli while maintaining the spatial specificity of information (*segregation*), as well as circuits which (b) transfer processed tactile information to neighboring columns for a context-dependent *integration*. *Segregating* and *integrating circuits* in combination (Tononi et al. 1998) should allow the recognition of objects (''what'') as well as a spatial orientation (''where'') and in combination the spatiotemporal context (''when'').

Comparison of different methods used to study layer- and cell-type specific cortical connectivity

Details of our experimental approach and the controls that have been performed in order to specifically map monosynaptic connections with a sublaminar resolution can be found in two methodological papers (Kötter et al. 1998, 2005) and several original research reports (Schubert et al. 2001, 2003, 2006). Here we briefly present the essential features of our technique to compare them to other methods commonly used to study cortical connectivity. The German Law on the Protection of Animals was strictly followed in all experiments.

Juvenile male rats were used as experimental animals (postnatal days 17–23). After decapitation, acute coronal slices of 300 μm thickness containing the primary somatosensory (barrel) cortex were cut on a vibratome. The experiments were performed at an Infrapatch-setup (Fig. 2a), modified for uncaging experiments (see below). The slices were introduced to the recording chamber which was decoupled from the motorized platform of a fixed stage microscope. In the acute slice, with the help of Dodt-quarterfield illumination and infrared contrast enhancement (Dodt and Zieglgänsberger 1994), a specific excitatory neuron in the layer of interest located in a barrel-related column was selected for whole-cell recording with biocytin-containing patch electrodes (Sakmann 2006).

After characterizing the intrinsic (e.g., action potential discharge pattern) and extrinsic synaptic properties of the neurons, γCNB ''caged'' glutamate was added to the recirculated artificial cerebrospinal fluid (ACSF) initially at a concentration of 1 mM, later 0.5 mM. This photolabile substance releases active glutamate upon application of UV light from its molecular cage which is capable to excite all neurons in the stimulated target field (Callaway and Katz 1993). The UV flash light was guided via the epifluorescence port of the microscope and focused with the aid of a rectangular aperture and the 40× objective on a 50×50 μm^2-large area ~50 μm below the slice surface.

Each recorded neuron was mapped for its afferent functional synaptic connectivity in a cortical area containing all six layers and at least two neighboring columns. For this purpose the microscope was moved in a computer-

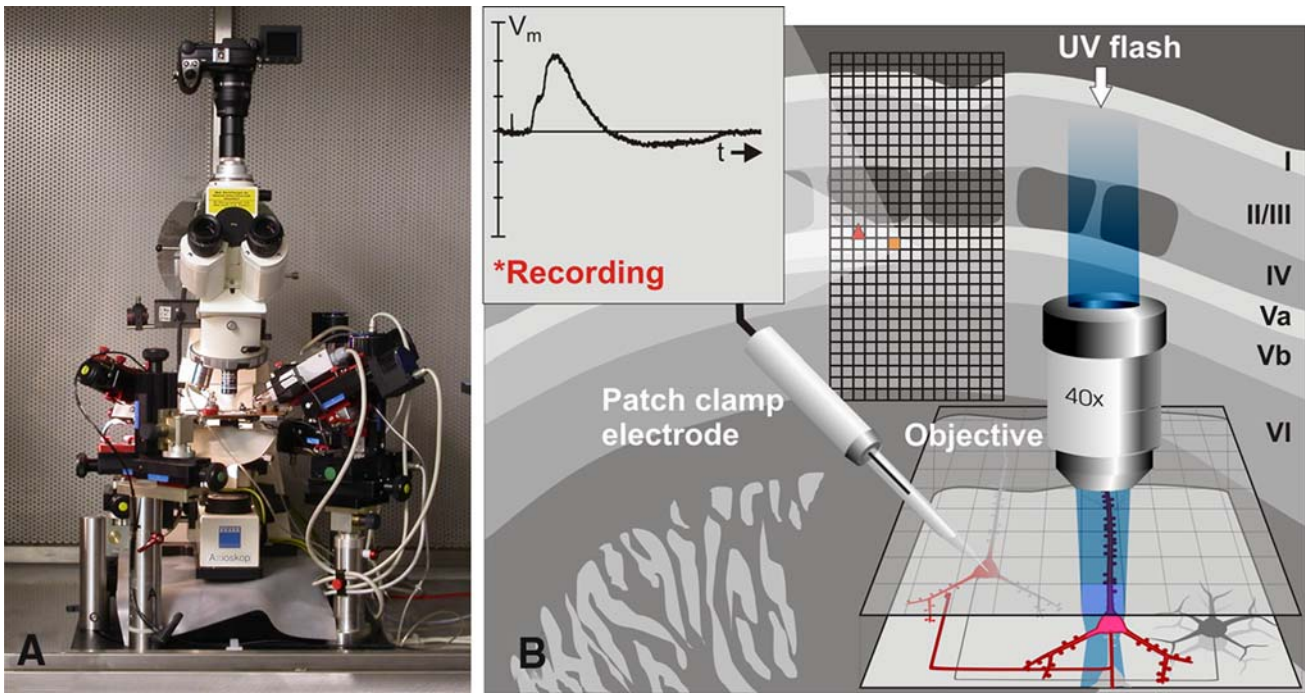

Fig. 2 Setup and basic experimental approach. **a** Photograph of the set-up. **b** Schematic representation of the mapping experiments. In the *foreground* a patch-clamp electrode records from a visually identified target cell in a specific layer of interest (here: *red triangle* in layer Va) and at the same time the objective focuses a UV-flash on a 50×50 μm^2-large area in layer Va in which glutamate is released from its photolabile molecular cage (*orange square* as a color code of the input strength). This excites a pyramidal cell to fire an action potential, which can be recorded in the target cell as an EPSP (inset *recording*). In the *background* a drawing of the slice including its layers and barrels is shown in *gray*, together with the dimensions of the mapped cortex consisting of *ca*. 450 areas covering all layers and two barrel-related columns (*black grid*)

controlled manner relative to the slice which rested in the recording chamber. Up to 500 different sites were stimulated consecutively by uncaging glutamate in the first studies every 10 s, later 5 s (Fig. 2b). Time locked to each flash stimulus the membrane potential of the patched neuron, which was held depolarized at –60 mV using slow voltage-clamp controlled current-clamp technique, was recorded for incoming excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs). These PSPs represent the physiological correlates of synaptic connectivity of neurons located at the flashed field with the neurons recorded in the different experiments (Fig. 2b). The localization and the strength of the PSPs, after correction for spontaneous events and possible direct flash-induced responses of the recorded neurons, were used to construct color-coded maps showing the layer- and column-specific monosynaptic functional connectivity of one recorded neuron. After the completion of the mapping, slices were fixed and neurons filled with biocytin were revealed histochemically. In addition, the barrels were labeled by cytochrome oxidase-histochemistry, and the patterns were compared to the native slice which usually was in good agreement. All neurons were reconstructed three-dimensionally and quantitatively evaluated with the aid of the Neurolucida system. Finally, either the micrographs of the native slices or their respective graphical representations were overlaid with the size-corrected reconstructions of the respective biocytin-filled neurons as well as with the specific functional connectivity maps. The quantitative analysis of these maps provided the basis for determining and comparing the functional connectivity of defined cell classes. For this we especially focused on the average layer and column-specific spatial distribution of origins as well as the average strength of intracortical synaptic inputs (see also Fig. 4).

What is the advantage of glutamate uncaging (Fig. 3b) for establishing cortical connectivity in comparison to previously used methods of analyzing cortical connectivity, as for example electrical stimulation (Fig. 3a) or paired recordings (Fig. 3c)? Electrical stimulation is not suitable for our purpose, since only one or a few sites can be stimulated without lesioning the tissue. Furthermore, due to the diffuse and hardly controllable extension of the stimulated field and the additional excitation of fibers-of-passage, the spatial control of the stimulation site is very poor with electrical stimulation. In contrast, paired recordings of synaptically connected neurons provide access to very detailed information of the unitary properties of the connection and their short-term plasticity (Thomson and Deuchars 1994; Feldmeyer et al. 1999). Since both, the pre-

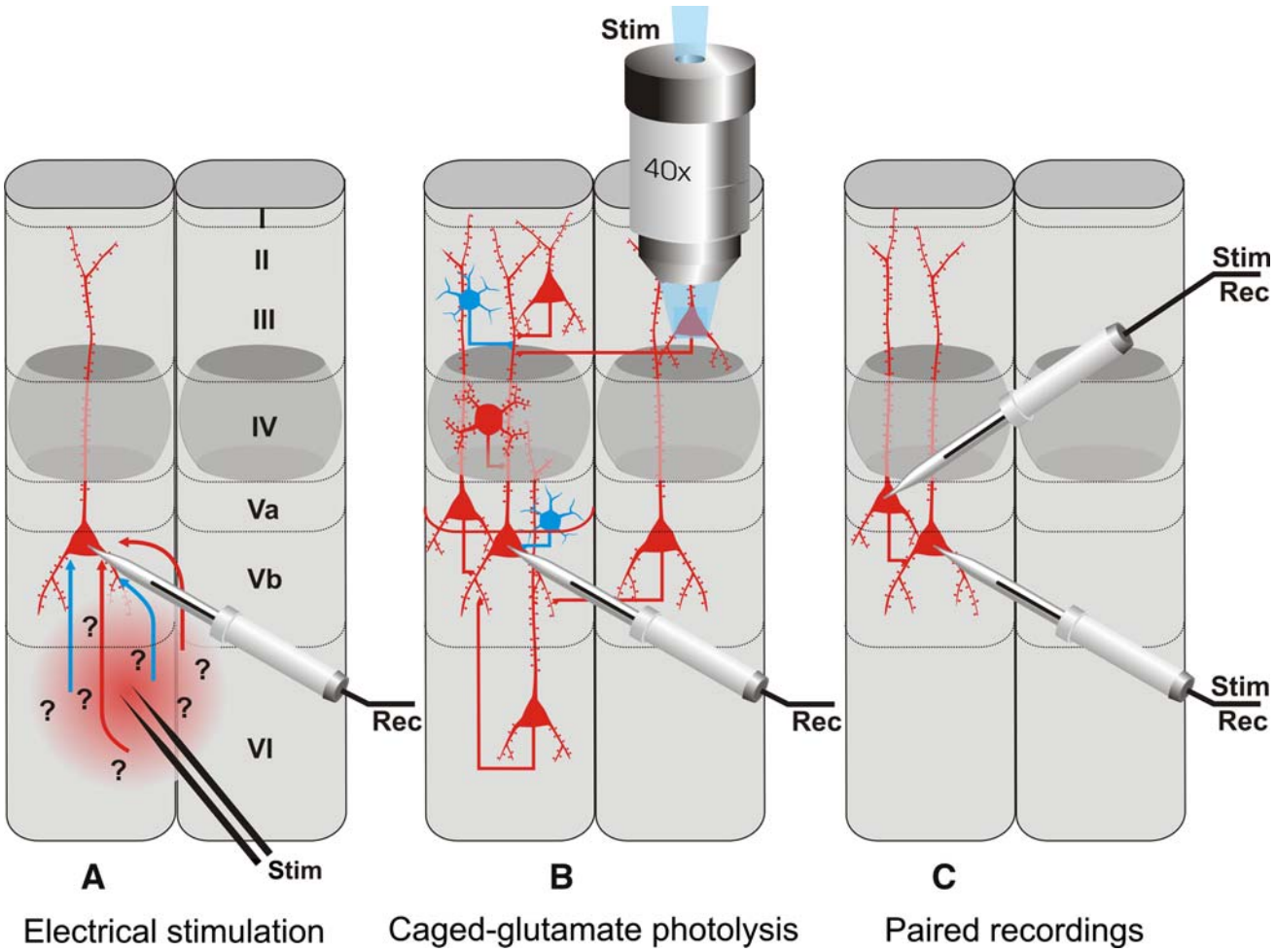

Fig. 3 Comparison of the three most frequently used methods to analyze cortical synaptic connectivity. **a** Electrical stimulation (*stim*) of one or a few spots in a certain layer of the cortex with a bipolar electrode and whole-cell recording with a patch pipette (*rec*, holds for all panels). Here a large number of excitatory and inhibitory neurons and fibers-of-passage are stimulated with poor spatial control. During recording stimulus position can only be changed by inserting the electrode at different places which always will cause a small lesion. **b** Photo-chemical stimulation by flash release of glutamate, by contrast, enables to specifically stimulate a small number of excitatory and inhibitory cells at sublaminar resolution. All layers and several columns can be specifically stimulated while recording from the same neuron of interest. **c** Paired recordings allow the stimulation of a single (or very few) presynaptic neuron(s) with exquisite temporal and spatial control. The unitary properties and the subcellular location of the synapses of such a connection can be determined; however, the overall picture of connectivity for both local and especially more distant sites can only be approximately reconstructed from an extensive series of experiments

and the postsynaptic neuron can be stained, the number and location of the synapses responsible for the established functional properties can be determined as well. This is unfortunately not possible with the uncaging technique. However, it has the great advantage that many more presynaptic sites containing thousands of neurons can be investigated than with the paired recording approach.

In addition, with paired recordings one is usually restricted to studying neurons that are very closely located to each other, and only a few neurons (the highest published number being 4; (Gupta et al. 2000) can be examined in one experiment. These spatial and numerical limitations make it impossible to obtain the complete picture of the entire pattern of connectivity, especially of the transcolumnar, in a single column (which is estimated to consist of some 10,000 neurons) in a single preparation. For this reason it is desirable to also use a complementary method like computer-controlled mapping of functional connectivity with sublaminar resolution by uncaging glutamate. By rigorous calibration of stimulus strength it is possible to analyze the putative monosynaptic connectivity of all neurons contained in all layers of at least two cortical columns with a spatial specificity comparable to those of paired recordings. Ultimately it is desirable to combine both methods in a single experiment as in principle accomplished by Yoshimura et al. (2005).

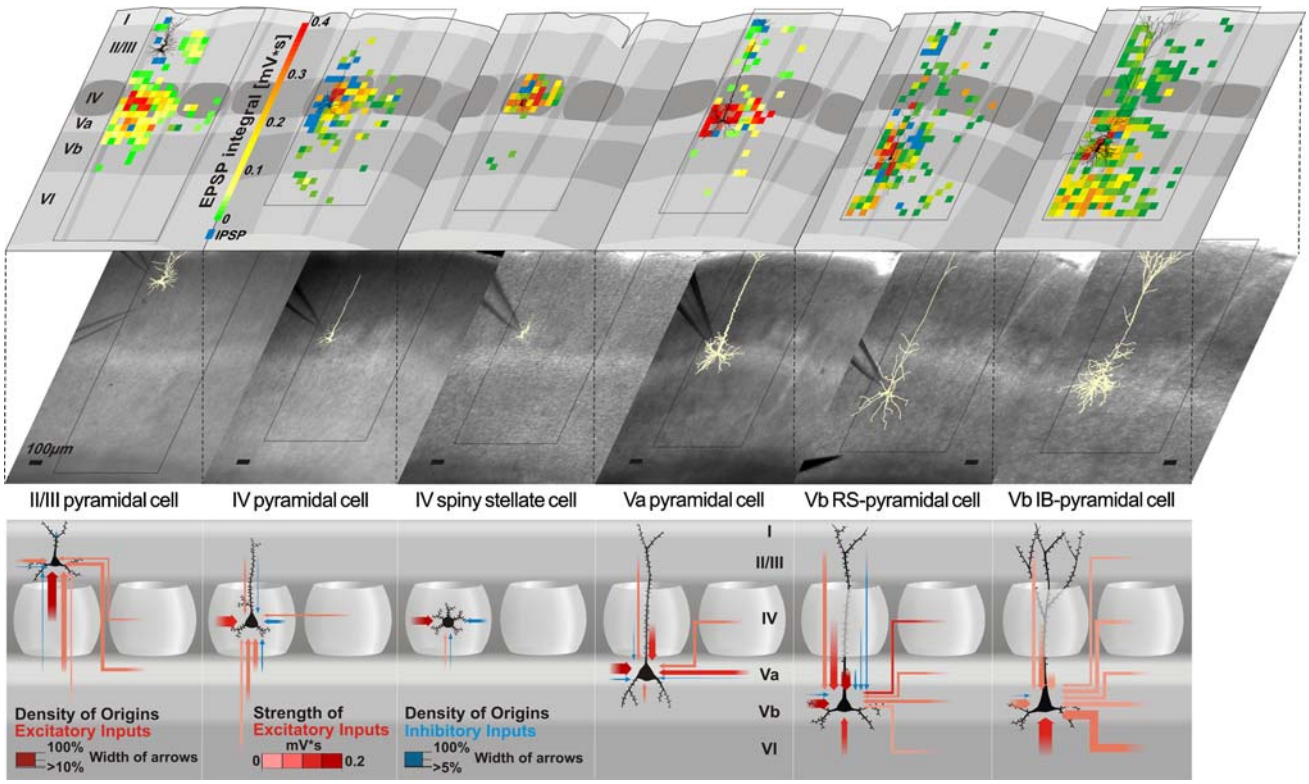

Fig. 4 Overview of all excitatory neurons examined for their functional monosynaptic intracortical connectivity in the different cortical layers. ***Top panel*:** Color-coded maps of the position and strength of monosynaptic EPSPs (in *green* to *red*, see scale to the *left* showing the EPSP integral in mV*s) and position of IPSPs (in *blue*). In *gray* the dimensions of the cortical layers and barrels are delineated according to the appearance of the native slice and post hoc cytochrome oxidase stainings. The respective recorded neuron is shown as a reconstruction in the ***middle panel***. It is overlaid there on the micrograph of the acute slice with the patch pipette left in place after the mapping of the functional connectivity. Note the barrel pattern in layer IV. *Scale bar*: 100 µm. ***Lower panel*:** Diagrams of afferent connectivity based on quantitatively analyzed and statistically evaluated data. The strength of the excitatory inputs is coded by the different red color intensities. The density of the excitatory (*red*) and inhibitory inputs (*blue*) is represented by the thickness of the arrows (see calibration information to the *left*). Positioning of the *arrow heads* close to the soma is only for the sake of simplicity and does not suggest that synapses were located there exclusively or preferentially

Layer- and cell type-specific circuits of cortical excitatory neurons

In the following we will present the different excitatory neuron classes and their functional capabilities in an order that follows the so-called canonical microcircuit of the cortical column (Douglas and Martin 2004). The thalamus preferentially projects into layer IV and, as an extreme simplification, starts there a sequence of cortical processing of sensory information. In this model, intracortical signal processing is assumed to happen in a number of steps, which includes a projection from layer IV to layers III and II as well as from those supragranular layers to the infragranular layers V and VI. From there, the projection neurons of these layers reach various cortical and subcortical target areas (see also Introduction). Details that go beyond the key findings described in the following sections can be extracted from Fig. 4 and our recent publications (Schubert et al. 2001, 2003, 2006).

The intracortical functional connectivity of excitatory neurons of the lamina granularis (IV)

The coexistence of pyramidal neurons and excitatory spiny stellate cells in layer IV has been known for a long time (Jones 1975). However, during our studies of this layer we were able to distinguish three morphologically different classes of spiny neurons (Staiger et al. 2004). Specifically, we provided evidence of a cell type specific functional connectivity for spiny stellate cells on one hand and for star pyramidal cells and classic pyramidal cells on the other hand (Schubert et al. 2003).

Layer IV spiny stellate cells

This cell type shows the least extensive intracortical connectivity of all neurons investigated so far. The origins of excitatory and inhibitory inputs of this type of neurons were very numerous (dense) and mainly restricted to their

own layer, i.e., the confines of the home barrel. The excitatory inputs were very strong which was ascertained by high-integral values of all incoming excitatory postsynaptic potentials (EPSPs) within 150 ms reflecting large amplitudes and/or high numbers of the PSPs. In perfect agreement with paired recording studies by Feldmeyer et al. (1999), Petersen and Sakmann (2000), this is a sign of a dense and efficient local synaptic network of these neurons, which could serve to amplify the numerically weak thalamic inputs (Hersch and White 1981). Altogether, the spiny stellate cells clearly seem to maintain a segregation of tactile information.

Layer IV star pyramidal and pyramidal cells

For reasons of simplification these cells are referred to as pyramidal cells here (see also Staiger et al. 2004). These cells can be treated collectively since they are not significantly different with regard to their intracortical functional input connectivity. Their relatively strong and dense local circuits were similar to those of the spiny stellate cells. However, these pyramidal neurons showed two additional connectional characteristics that had not been highlighted by others but which should have important functional consequences: (a) they consistently obtained translaminar intracortical inputs from all other layers of their home column and (b) in 80% of all cases surprisingly clear transcolumnar inputs from the adjacent barrel could be found. That means that pyramidal cells of layer IV, contrary to earlier findings (cf. Goldreich et al. 1999; Petersen and Sakmann 2001; Laaris and Keller 2002), but in agreement with elegant recent in-vivo pharmacology (Fox et al. 2003), make up a first correlate for circuits that integrate ''top down''-information from hierarchically higher layers (supra- and infragranular layers) and are capable to perform context-dependent tactile information processing (Gilbert 1998).

The intracortical functional connectivity of pyramidal cells of the lamina pyramidalis (III) and corpuscularis (II)

These so-called supragranular layers contain pyramidal cells as excitatory neurons. Because of their proximity to the pial surface, the cells of the upper part of the supragranular layers show distinct deformations of their apical dendrites such as early tuft formation or an oblique course of the main stem(s) (Feldmeyer et al. 2006; Staiger et al. 2006). However, as being typical of all sensory cortices the two supragranular layers of the rodent cortex cannot readily be distinguished on cytoarchitectonic grounds. Pyramidal cells of supragranular layers commonly showed local, intralaminar inhibitory inputs as a characteristic of their functional connectivity. Their local, intralaminar excitatory inputs were, however, surprisingly weak (Feldmeyer et al. 2006) and relatively scattered (Holmgren et al. 2003). In contrast, the predominant source of excitatory inputs for all pyramidal neurons of the supragranular layers was layer IV of their home column (Feldmeyer et al. 2002). The frequent observation of excitatory inputs also from layer IV of neighboring columns supports the earlier hypotheses that oblique projections from layer IV neurons into the neighboring supragranular layers could be a route for integrating sensory information transcolumnarly (Fox 2002). Apart from this consistently strong layer IV to II/III pathway, ~50% of the supragranular pyramidal neurons also received strong and extensive inputs from layer Va, which places these neurons in a position to integrate inputs from layers IV and Va, both from the home and the neighboring columns. It was thus hypothesized that these pyramidal cells are another important cortical interface of the lemniscal and paralemniscal pathways (Ahissar et al. 2000; Shepherd and Svoboda 2005; Schubert et al. 2006).

Altogether, our findings and those of others, very clearly confirm the initial major layer IV-to-II/III step of the canonical circuit of the column, cited above, which has so far been based on indirect data. Furthermore, our unpublished observations on axonal projection patterns of ''true'' layer II or ''true'' layer III pyramidal cells, foster the concept that layer III pyramidal cells are preferentially participating in intracolumnar circuits, therefore segregating tactile information, whereas layer II pyramidal cells are preferentially involved in cross-column integrating ensembles. Similar findings have been reported for rat visual cortex (Hellwig 2000) and mouse barrel cortex (Larsen and Callaway 2006).

The intracortical functional connectivity of pyramidal cells of the lamina ganglionaris (Va)

Layer Va had—if at all—only rarely been considered as a genuine layer (Ahissar et al. 2000; Manns et al. 2004). It was generally regarded as a cell sparse variant of layer Vb, which was considered representative for the entire layer V. Our investigations, however, unambiguously showed that layer Va is much better classified as an independent cortical layer (Schubert et al. 2006). Morphologically, layer Va pyramidal cells exhibit a very homogeneous architecture. Electrophysiologically we found comparable numbers of ''regular spiking'' and ''intrinsically burst spiking'' pyramidal cells. However, since these electrophysiological classes neither correlated with the neurons' morphology nor with their functional connectivity, they will be presented as a single group.

Most striking here was the strong innervation of these neurons—intracolumnarly *and* transcolumnarly—by neurons of their own layer. This horizontal intralaminar con-

nectivity was most distinctive for this cell type. Only in this layer the same cell type is participating both in segregating and integrating circuits, if these can be differentiated here at all. This also corresponds well with earlier and more recent in vivo electrophysiological analyses (Armstrong-James et al. 1992; Derdikman et al. 2006). Additionally, we found that Va pyramidal cells are strongly innervated by excitatory neurons located in the barrel of the corresponding column. Interestingly, the existence of this particular microcircuit has recently been confirmed independently by paired recordings (Feldmeyer et al. 2005). So these neurons can functionally be characterized as an early cortical interface: they merge ''lemniscal sensory information'' which is mainly supplied to layer IV by the ''specific'' thalamic nucleus (*Nucleus ventralis posteromedialis*), and ''paralemniscal information'' which is supplied into layer Va by the ''unspecific'' thalamic nucleus (*Nucleus posterior thalami, pars medialis*) (Kleinfeld et al. 2006; Bureau et al. 2006). We will refer to this in greater detail at the end of the Discussion.

The intracortical functional connectivity of pyramidal cells of the lamina ganglionaris (Vb)

In contrast to the pyramidal cells of layer Va, the pyramidal cells of lamina Vb show a consistent correlation of morphological, electrophysiological and functional connectivity characteristics that clearly separate two distinct populations of excitatory neurons (Schubert et al. 2001; see also Chagnac-Amitai et al. 1990; Larkman and Mason 1990; Mason and Larkman 1990; Hefti and Smith 2000; Molnar and Cheung 2006).

Layer Vb RS-pyramidal cells

A sparsely branched dendritic tree with a small tuft in layer I, is a typical morphological feature of these neurons. Concerning their functional connectivity, it is striking that, within their own column, they show a patchy, hot-spot like pattern of strong excitatory and numerous inhibitory inputs from all cortical layers. Apart from prominent local excitatory inputs EPSPs, which are induced by the stimulation of layers IV and Va, are dominant here. Thus, this class of pyramidal cells seems to be capable of processing and filtering information within one column most effectively.

Layer Vb IB-pyramidal cells

In comparison to Vb-RS pyramidal cells, these impressive neurons—partly reminiscent of Betz and Meynert giant pyramids—with their intensely branched dendritic tree show four characteristics: (a) especially dense, but on average weaker excitatory inputs from all layers, (b) a noticeably high number of EPSPs from lamina VI (which is unique compared to all other investigated neurons), (c) an extensive transcolumnar functional connectivity, and (d) strikingly few inhibitory inputs. Therefore, the characteristics of Vb IB pyramidal cells in intracortical circuits provide a plausible basis for integrating the information of various adjacent columns—and thus whiskers (Ghazanfar and Nicolelis 1999; Staiger et al. 2000b; de Kock et al. 2007).

For this reason, although at a different layer-dependent level of complexity when compared to the connectivity of the other layers described so far, the population of Vb RS-pyramidal cells could be referred to as ''segregators'' the one of Vb IB-pyramidal cells as ''integrators'' of tactile information located within a single layer of barrel-related columns.

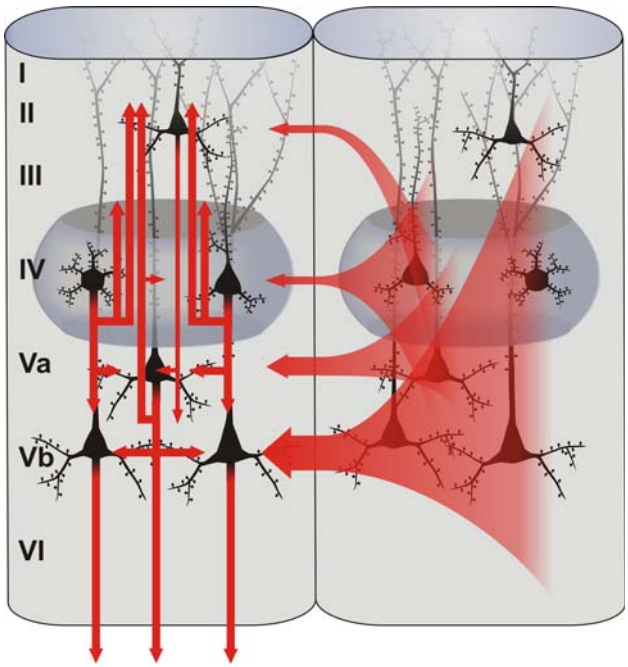

Fig. 5 Summary diagram of the core features of cortical columnar connectivity for segregation and integration of sensory information as derived from our mapping studies. Intralaminar connections and less prominent translaminar or transcolumnar pathways are not shown to not obscure the main findings. *Arrows* within the *left* column signify the main features of translaminar intracolumnar connectivity and the corticofugal projections of the infragranular pyramidal cells. The *shaded* transcolumnar projections display the main laminar sources of context information from neighboring whiskers originating from neighboring columns. Note that layer Vb receives the most extensive transcolumnar input and that also direct barrel to barrel connections do exist, although they are relatively sparse and cell type-specific

Functional consideration

The synopsis of our studies gives rise to a comprehensive picture of the basic circuits in which excitatory neurons

are integrated in the functional module of the *cortex cerebri*, i.e., the cortical column. If we—for reasons of clarity—only discuss the key results of our experiments, two major principles of connectivity can be generalized. They are sufficiently illustrated by the two phrases ''layer specificity precedes cell type specificity'' and ''segregation and integration of sensory information occur in parallel''.

Even if one considers only excitatory neurons it becomes apparent that within one cortical column multiple parallel and interacting circuits must be existent, which have not yet been understood very well (Fig. 5; see also Thomson and Bannister 2003; Douglas and Martin 2004; Silberberg et al. 2005; Bureau et al. 2006; de Kock et al. 2007). However, it has already been proposed that the characterized circuits could conceivably instantiate the key functions of sensory cortices mentioned in the Introduction (see Fig. 1). On the one hand, the segregational organization of neurons in layers IV (spiny stellate cells), supragranular layers II/III (a population of pyramidal cells receiving weak inputs from layer Va; D. Schubert et al., unpublished observations) and Vb (RS-pyramidal cells) enable that the local specificity of a tactile stimuli is maintained to a relatively high degree. Segregation of information is a pre-condition for identifying the location of different stimuli in space (''where''). On the other hand, conceivably by sacrificing spatial specificity, the integrating neurons in layer IV (star pyramidal and pyramidal cells), layer II/III (a population of pyramidal cells receiving strong layer Va inputs; D. Schubert et al., unpublished observations) and layer Vb (IB-pyramidal cells) can identify the coincidence of object features across different locations. This integration of information (and subsequent comparisons) is very likely relevant for the recognition of objects (''what''). Both circuits would need to interact providing both highly resolved spatial information and object identification to identify the spatiotemporal context of object features (''when''). With regard to this, the topographical representation of the receptor surface could be a fundamental advantage in order to attain short distances for fast processing, especially between those neurons for which—due to neighbor relationships of the corresponding peripheral receptors—a preferred interaction can be expected (Kaas 1997). This is thought to be an important prerequisite for several types of tactile information coding (Diamond et al. 1999; Kleinfeld et al. 2006).

In view of this concept, what is special about lamina Va? The principle of layer specificity is without any doubt valid here (Manns et al. 2004; Schubert et al. 2006; Derdikman et al. 2006). Cell type-specificity, however, could not be found. It would be possible, though, that the pyramidal cells of layer Va with their uniform functional connectivity are linking segregating and integrating circuits in a way that is not yet well understood. Such a higher order specificity might have its correlate in parameters not examined here, like for instance the short-term dynamics of the synapses involved or their location in the dendritic tree (Thomson and Deuchars 1994).

An alternative hypothesis is that layer Va-associated circuits add a different aspect of sensory information processing, e.g., the ''when'' coding to the ''what'' and ''where'' information. Neurons of layer Va might indeed obtain and process differently coded tactile information. This hypothesis is based in part on morphological findings, which show that lamina Va is the major target layer for projections coming from the *Nucleus posterior thalami, pars medialis* (Lu and Lin 1993). This nucleus is the thalamic constituent of the paralemniscal system, which was initially regarded as a system to code ''where''-aspects by Ahissar et al. (2000). This can still be related to the ''when''-aspect postulated here: the way of ''where''-detection postulated for the paralemniscal system is to code when which vibrissa has been touched within a so-called ''whisking cycle'' (the active movement of the vibrissae), meaning a temporal coding of spatial information (Kleinfeld et al. 2006). Newer concepts of Derdikman et al. (2006) also favor the ''when''-coding by the paralemniscal pathway. What we and others (Bureau et al. 2006) have shown is that the target cells of the paralemniscal pathway in layer Va might effectively integrate inputs within the same layer (intra- and transcolumnarly) as well as from lamina IV (Feldmeyer et al. 2005) and that they transmit the processed information via their axonal projections to the other cortical layers, e.g., parts of the supragranular layers (Shepherd and Svoboda 2005).

Finally, for behaviorally relevant sensory signal processing not only interactions between the lemniscal and paralemniscal systems, but also with hierarchically higher cortical areas (e.g., secondary somatosensory cortex, parietal associative cortices) as well as with completely differently organized projection systems (cholinergic basal forebrain system etc.) will be necessary (Juliano and Jacobs 1995; Nicolelis et al. 1997; Kleinfeld et al. 2006). Whatever the specific content of the information is that is transmitted to the targets of cortical columns, the ''big integrators'' i.e., the layer Vb-IB pyramidal cells, also have to be considered as the main output neurons of the columns (de Kock et al. 2007; Schubert 2007).

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