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Experimental characterization and numerical modelling of synaptic connections in layer 2 and 3 of the primary somatosensory “barrel“ cortex of the rat

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The primary somatosensory representation in the cerebral cortex is thought to be mediated by thalamocortical afferents which predominantly excite neurons in the layers of one “cortical column”. One intracortical microcircuit, which is recruited in an early stage following thalamocortical activation, is thought to be the layer 4-to-layer 2/3 (L4-to-L2/3) intracortical intracolumnar microcircuit. It is comprised of an excitatory and an inhibitory pathway that are activated by L4 spiny neurons following whisker deflection and that converge onto L2/3 pyramidal neurons. It has been shown recently, that L2/3 interneurons classified as locally projecting *local inhibitors* based on their axonal projection receive strong excitatory input from L4. One explanation for the low firing rates in pyramidal neurons (0.2-0.4 APs per stimulus) observed *in vivo* is the synchronous activation of interneurons in L2/3 which could provide inhibition on L2/3 pyramidal neurons. While the excitatory synaptic connections contributing to the L4-to-L2/3 microcircuit have been characterized thoroughly, quantitative information on the L2/3 inhibitory connections within cortical columns and thereby the impact of L2/3 inhibition on signal representation in L2/3, remains unclear. Here, we investigated the synaptic connection between L2/3 *local inhibitors* and L2/3 pyramidal neurons within an anatomically defined cortical column using paired whole cell patch-clamp recording, followed by computer-aided reconstruction, and, subsequently, numerical simulations to recover the underlying synaptic conductance, thus closing the gap of information on inhibitory connections in the L4-to-L2/3 intracortical intracolumnar microcircuit.

Inhibitory postsynaptic potentials were measured in a total of 44 L2/3 interneuron-to-L2/3 pyramidal cell pairs (Mean amplitude -0.74 mV at a depolarized baseline potential of -57 mV). Fifteen of these pairs were identified as local inhibitors based on their axonal distribution largely confined to their home-columns. We found strong and reliable inhibitory synaptic transmission between these L2/3 *local inhibitors* and L2/3 pyramidal neurons located in the same cortical column averaging at about -0.9 mV at a depolarized baseline potential of -58 mV. On average, L2/3 *local inhibitors* made 5.5±1 synaptic contacts onto the basal dendrites of L2/3 pyramidal neurons (n=6). We determined the synaptic conductance per synaptic contact to be 0.9±0.3 using inverse modeling (n=6). The validity of inverse modeling results depends critically on the validity of the model assumptions. We therefore performed a sensitivity analysis to quantify the dependence of the obtained conductance estimates to errors made in assumptions about model parameters. This analysis demonstrated that the conductance estimates were rather robust to perturbations in model parameters (membrane capacitance, membrane resistance, axial resistivity, synaptic reversal potential, number of synaptic contacts). The location of synaptic contacts on L2/3 pyramidal neuron basal dendrites matched the location of synaptic contacts from L4 spiny neurons onto L2/3 pyramidal neurons. Given a near-synchronous activation of these connections, inhibition of L2/3 pyramidal neurons might be

mediated by spatial and temporal proximity of inhibitory and excitatory contacts (shunting inhibition) rather than by simple summation at the soma. We therefore conclude that the synaptic circuit from L4 to L2/3 may provide efficient shunting inhibition that is temporally synchronized with the excitatory input from L4 to L2/3. The data from the present study closes the gap of information on inhibitory contributions to the L2/3-to-L4 intracolumnar intralaminar microcircuit. To investigate the effect of stimulus-evoked activity in the entire L4-to-L2/3 circuit, however, larger numerical models of this microcircuit will be required that implement the experimentally found constraints on anatomical connectivity, electrical excitability and synaptic properties.