Cellular and network mechanisms of cortical processing of tactile inputs

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In our group we investigate the mechanisms that shape the response of cortical neurons to sensory stimulation. The vibrissal system of rodents is gradually becoming a standard model for studying sensory systems, both at the anatomical, physiological and behavioral levels. Rats are nocturnal animals with poor sight and they are using their whiskers as one of the primary means to gather information on their environment. To collect information rats sweep their whiskers against objects at frequencies of 5-20 Hz. The barrel cortex is the first cortical stage of processing of tactile information. Inputs from the whiskers are transmitted through three different thalamic pathways to the cortex where they activate mostly neurons in layer 4. In the barrel cortex neurons are clustered topographically according to whisker arrangement in the mystacial whisker pad. The majority of the neurons in the cortex are excitatory (80-85%). On average each cortical cell makes reciprocal connections with thousands of other neurons. The response of a cortical neuron to stimulation involves, therefore, complex feedforward and feedback interactions (Figure 1A). In most studies of sensory processing extracellular recording are used. Since in these recording technique spikes are recorded, it allows to probe only the output signals of the cells. In most of our studies, however, we record the membrane potential of neurons using patch or sharp electrodes.

By recordings the membrane potential of neurons in the living animal one can probe the underlying synaptic inputs of the cell and therefore to reveal the mean network activity. Because of the high mechanical stability that is required to achieve stable recordings only small number of laboratories worldwide uses this technique in the intact animal. In particular, we study the way excitatory and inhibitory inputs interact and relate to each other to shape the response of cortical cells to sensory stimulation and how they determine the activity during periods when stimulation is absent. To evoke response in neurons of the barrel cortex the whiskers are stimulated by special piezoelectric devices while the membrane potential is recorded (Figure 1B).

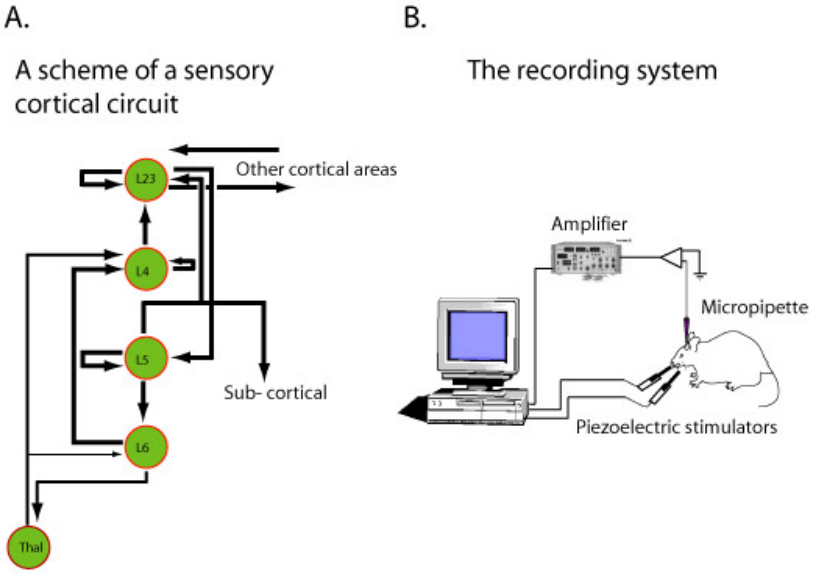

Fig. 1 *Cortical column and experimental setup*
A) Schematic representation of the main circuits in a cortical column. Note that in addition to strong feedforward inputs (from the thalamus to layer 4 and further to all the other layers) there are strong feedback connections to layer 4 and also from layer 6 to the thalamus.
B) Electrical signals are recorded using glass micropipettes ("patch electrodes"), amplified and stored by the computer that also controls the piezoelectric devices used for mechanical stimulation of the whiskers.

In recent years we have studied different processes in the barrel cortex, a partial list of selected projects is listed below.

Instantaneous correlation of excitation and inhibition in-vivo

Temporal and quantitative relationships between excitatory and inhibitory inputs in the cortex are central to its activity, yet they remain poorly understood. In particular, a controversy exists regarding the extent of correlation between cortical excitation and inhibition. While some models suggest that these inputs reflect independent random walk processes, others suggested tight correlation between excitation and inhibition. So far this question was not addressed simply because single cell recordings, even when intracellular recording is used, can not reveal excitation and inhibition simultaneously. Using simultaneous intracellular recordings in pairs of nearby neurons *in-vivo*, we show that during spontaneous and sensory evoked activities in the rat somatosensory cortex, excitatory and inhibitory inputs are continuously synchronized and correlated in strength (Figure 2).

Dynamics of excitation and inhibition during sensory adaptation

Sensation often involves repetitive or sustained stimulation of sensory organs, which result in adaptation of neuronal responses along the sensory pathway. Since the effect of sensory adaptation on excitatory and

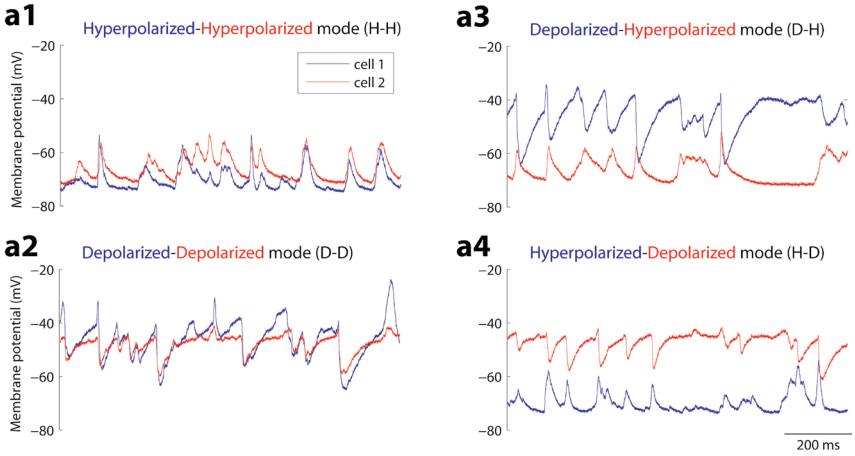

Fig. 2 *Excitatory and inhibitory synaptic potentials of nearby neurons are synchronized during spontaneous activity. Each cell is color coded.*
a1-a4) Simultaneous recordings from two cortical cells at 4 different combination of current injection (H-H, D-D, D-H, and H-D). Depolarization of the cells was sufficient to reveal inhibitory synaptic potentials in a2-a4.

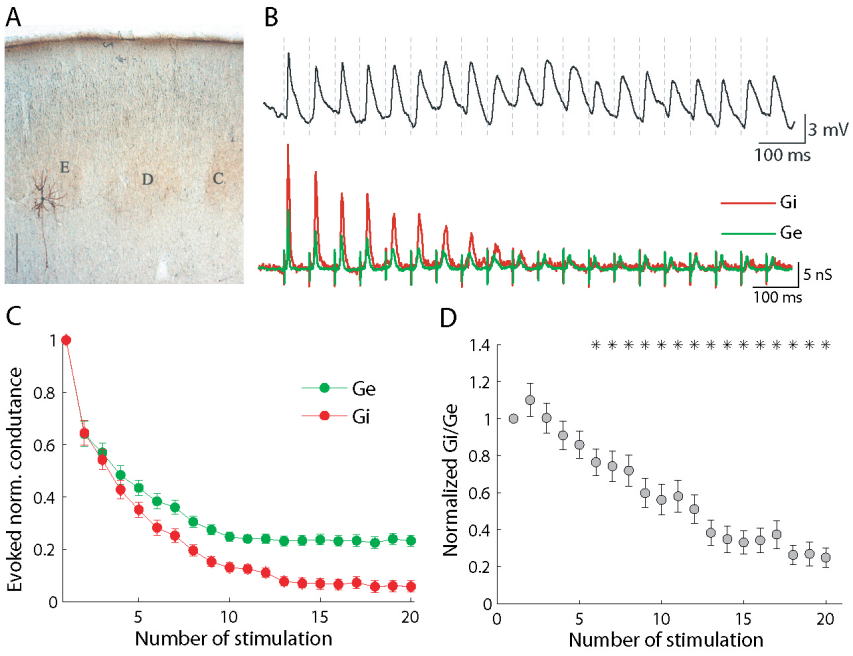

Fig. 3 *Change in the balance between excitation and inhibition during repetitive stimulation.*
A) Reconstructed spiny stellate cell inside barrel E at layer 4.
B) Upper trace: Average membrane potential of the cell under repetitive sensory stimulation at 18 Hz. Dotted lines denote a whisker deflection. Lower traces: Estimation of the excitatory (Ge) and inhibitory (Gi) conductance evoked by sensory stimulation.
C) Popoulation average (N=34 layer 4 neurons) of the maximal evoked excitation and inhibiton after each whisker deflection. Error bars denote SEM.
D) Population average of the ratio Gi/Ge for each whisker deflection. Asterisks denote significant difference with respect to the first deflection (p-value<0.01).

inhibitory inputs of cortical neurons is poorly understood, we studied how repetitive whisker stimulation affects the dynamics of evoked excitatory and inhibitory conductances which were measured by performing patch recordings in the barrel cortex of anesthetized rats. Inhibition adapted more than excitation, which skewed the balance towards excitation, and enhanced synaptic potentials at steady state despite a large adaptation in excitation (Figure 3). We suggest that differential adaptation of excitation and inhibition may increase the throughput of sensory information into the cortex.

Stimulus specific adaptation

Neurons in the barrel cortex and the thalamus respond preferentially to stimulation of one whisker (the principal whisker) and weakly to several adjacent whiskers. Cortical neurons unlike thalamic cells gradually adapt to repeated whisker stimulations. The aim of this intracellular study was to determine whether the response of a cortical cell to stimulation of an adjacent whisker would be affected by prior adaptation induced by stimulation of the principal whisker, and vice versa. Employing a high-frequency stimulation that causes substantial adaptation in the cortex, we show that cortical adaptation evoked by a train of stimuli applied to one whisker does not affect the synaptic response to subsequent stimulation of a neighboring whisker (Katz et al., 2006). Our data indicate that intrinsic mechanisms are not involved in cortical adaptation. Thalamic recordings obtained under the same conditions demonstrated that an adjacent whisker response was not generated in the thalamus, indicating that the observed whisker-specific adaptation results from different adaptation pathways for neighboring whiskers, probably due to diverging thalamic inputs or from cortical integration.

Neuronal code and spatiotemporal repeating patterns of activity

It was recently discovered that subthreshold membrane potential fluctuations of cortical neurons can precisely repeat during spontaneous activity, seconds to minutes apart, both in brain slices and in anesthetized animals (Ikegaya et al., 2004). These repeats, also called cortical motifs, were suggested to reflect a replay of

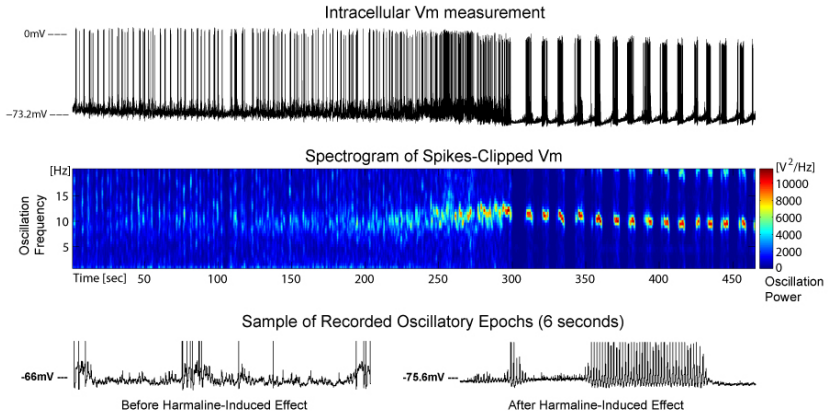

Fig. 4 *Harmaline-Induced Changes in the Oscillatory Activity of IO Neurons. Harmaline (10-20ug/kg) was injected IP while an IO neurons was recorded intracellularly (Top). A marked transition in both subthreshold oscillation and spike patterns is clearly visible after 5 min following the injection (in t=0). Spectral analysis of the membrane voltage (Middle) reveals enhanced oscillation power accompanied with narrowing of frequency distribution around 9-10Hz. Zooming in on sample oscillatory epochs before and after the induced changes (Bottom) exemplify the enhancement of epoch length, the reduction of oscillations between epochs.*

sequential neuronal firing patterns. In a recent study (Mokeichev et al., 2007) we searched for motifs in spontaneous synaptic activity, recorded from the rat barrel cortex and from the cat striate cortex of anesthetized animals, and found numerous repeating synaptic patterns of high similarity and repetition rates. To test their significance, various statistics were compared between physiological data and three different types of stochastic surrogate data that preserve dynamical characteristics of the recorded data. We found no evidence for the existence of deterministically generated cortical motifs. Rather, the stochastic properties of cortical motifs suggest that they are bound to appear by chance, as a result of the constraints imposed by the coarse dynamics of subthreshold ongoing activity.

Possible role of subthreshold oscillations in the inferior olive

In addition to our studies of the somatosensory cortex we explore the electrical properties of neurons in the olivo-cerebellar system. Subthreshold oscillation of the membrane potential is a prominent feature of inferior olive (IO) neurons which provides one of the major inputs to the cerebellum. For many years these oscillatory behavior was shown in brain slices but no direct evidence was found for their existence *in-vivo*. Recently, we showed that subthreshold oscillations are present also in the intact animal (Chorev et al., 2007). While oscillatory activity persists continuously in brain slices, we found that oscillatory activity *in-vivo* is a complex process that involves fast and slow rhythms.

Currently we study the possible role of IO neurons in essential tremor (ET) disorder. ET is a common movement disorder that affects up to 5% of the adult population. There is evidence to suggest that the tremor is caused by activity changes in the IO. Harmaline a MAO inhibitor can cause both sustained oscillatory activity in olivary neurons *in-vitro* and tremor in animals and it is commonly used as a pharmacologically-induced model for ET. In a current study we have shown that harmaline causes a profound increase in the oscillatory activity of IO neurons, in-vivo (figure 4). We currently study the relationship between the effect of harmaline and tremor of muscles in lightly anesthetized rats. Our goal is to develop a method for early detection signs of tremor activity in attempt to improve the treatment of ET using deep brain stimulation (DBS).

To conclude, our main research goal is to understand the synaptic mechanisms that give rise to the response of cortical neurons to sensory stimulation. The sensory response is shaped by a delicate balance between excitation and inhibition in the cortex. According to our studies, this balance, in addition to its dependence on the presented stimulus, is also affected by the history of the external stimulation and by the spontaneous activity in the brain. The mechanisms that we have found in anesthetized animals are likely to be involved in cognitive functions of the brain.

Selected publications

Ikegaya, Y., Aaron, G., Cossart, R., Aronov, D., Lampl, I., Ferster, D. and Yuste, R. (2004) Synfire chains and cortical songs: temporal modules of cortical activity. Science, 304, 559-564.

Katz, Y., Heiss, J.E. and Lampl, I. (2006) Cross-whisker adaptation of neurons in the rat barrel cortex. J Neurosci, 26, 13363-13372.

Mokeichev, A., Okun, M., Barak, O., Katz, Y., Ben-Shahar, O. and Lampl, I. (2007) Stochastic emergence of repeating cortical motifs in spontaneous membrane potential fluctuations in vivo. Neuron, 53, 413-425.

Chorev, E., Yarom, Y. and Lampl, I. (2007) Rhythmic episodes of subthreshold membrane potential oscillations in the rat inferior olive nuclei in vivo. J Neurosci, 27, 5043-5052.

Acknowledgements

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