Karolinska Institutet

Institutionen för Neurovetenskap

The role of striatal inhibition in the processing of cortical neuronal avalanches

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hillarpsalen, Retzius väg 8.

Onsdagen den 30 Januari, 2013, kl 09.00

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Stockholm 2013

Summary

The brain is spontaneously active even in the absence of any obvious motor actions or sensory perceptions. This so-called resting or ongoing activity reflects neuronal interactions necessary for the brain to process past actions, allow for current inputs, and prepare for future decisions and responses. In cortex, more than a decade of research has shown that resting activity exhibits a truly complex organization that partially originates from the underlying anatomy but equally important emerges from neuronal dynamics at the systems level. For the basal ganglia, despite their important role in brain function such as preparatory movement control, the organization of resting activity is barely understood. The current work centers on how the striatum, which is the main input nucleus of the basal ganglia, processes the spatiotemporally complex resting activity of the cortex.

Without a clear understanding of the spontaneous activity that arises in cortex, it would have been daunting and – most likely – impossible to approach this question experimentally. However, a decade of research has shown that spontaneous activity in cortex is precisely organized and that it is this organization that optimizes cortical networks for information processing. Spontaneous activity in superficial layers of cortex can extend over large areas with amplitude fluctuations that span multiple orders of magnitude. This activity has been identified as so-called *neuronal avalanches*, diverse spatiotemporal neuronal activity clusters that follow a power law distribution in clusters size with an exponent close to –1.5. This power law reflects balanced activity propagation where the likelihood of activity to propagate to distant cortical sites is maximized while avoiding pathological activity explosion, e.g. epilepsy. These and related measures allow for an absolute and quantitative characterization of cortical activity at rest to which striatal activity can be compared. Anatomy suggests that striatal neurons might respond to cortical neuronal avalanches and the pattern of converging and diverging corticostriatal projections suggests that neurons in the striatal microcircuit might even recombine neuronal avalanche input. The main aim of this thesis therefore was to investigate whether and how the striatum processes fluctuating input with particular focus on cortical neuronal avalanches.

Cortical inputs, besides exciting striatal medium spiny (MS) projection neurons, which constitute about 95% of neurons in the striatum, also project to a relatively small number of striatal interneurons, the fast-spiking (FS) neurons. FS interneurons in turn provide feedforward inhibition to MS projection neurons. The first part of this thesis on striatal processing of cortical inputs thus examined the firing patterns of FS interneurons in response to cortical inputs. Using a combination of computational modeling and *in vitro* whole-cell recordings, it is shown that input to FS neurons strongly influenced their firing pattern and spike time reliability. FS neurons fired precisely timed action potentials with little trial-to-trial variability both *in vitro* and in the model in response to fluctuating input. In contrast, FS interneurons exhibited their well-known random stuttering discharge only for constant input. Our modeling results suggest that FS firing variability, such as observed in rodents *in vivo* or in organotypic cultures *in vitro*, most likely results from input fluctuations. Importantly, this suggests that the temporal organization of cortical input to FS interneurons, as present in neuronal avalanches, translates into corresponding temporally precise feedforward inhibition of MS projection neurons. Accordingly, the short-term depression of FS-to-MS synapses further facilitated the translation of input variability at FS interneurons into variability of postsynaptic responses in MS projection neurons.

The deep location of the striatum in the forebrain and the sensitivity of cortical avalanches to common anesthetics currently presents huge obstacles when trying to simultaneously record cortical avalanches and striatal dynamics with cellular resolution. A major aim of this thesis therefore was to establish an experimental model system to study cortico-striatal dynamics in the presence of cortical neuronal avalanches. I therefore grew organotypic cortex-striatum-substantia nigra pars compacta cultures on planar multielectrode arrays and recorded spontaneous activity simultaneously from cortical and striatal tissue. While cortical cluster sizes followed a power law distribution with an exponent close to –1.5, striatal dynamics were characterized by a power law distribution in cluster sizes with a more negative exponent close to –3. This difference was absent under conditions of epilepsy or global disinhibition, that is, when blocking inhibition in both cortex and striatum. Thus, the significantly more negative striatal exponent under cortical avalanche conditions indeed indicates qualitatively different dynamics between cortex and striatum. In fact, the striatal local microcircuit actively decorrelates cortical neuronal avalanche input. This was demonstrated by intracellular calcium imaging of striatal neurons combined with local blockade of striatal inhibition. Under normal conditions, neuronal firing in spiny projection neurons fluctuated significantly between neighboring neurons and also fluctuated strongly in time between successive cortical avalanche inputs. Removal of local striatal inhibition synchronized spontaneous spiking activity between striatal neurons and increased striatal firing, overall reducing temporal fluctuations in striatal output over time. Thus, acute removal of local striatal inhibition results in a homogenous, non-discriminatory following of striatal neurons to cortical avalanche inputs.

In conclusion, the results from this thesis suggest that the striatum pays attention to the complex spatiotemporal organization of resting activity in cortex. The locally and temporally diverse responses of striatal neurons crucially depend on the intact inhibitory striatal microcircuits. The computational results suggest that FS interneurons in principle are able to translate large fluctuations of cortical inputs into diverse and timely feedforward inhibition onto MS projection neurons, which might contribute to the active decorrelation. Alternatively, recurrent inhibition between MS projection neurons might play an important role in the striatal response to cortical resting activity. The precise contributions of these local inhibitory pathways to striatal resting activity have yet to be determined. These results clearly establish that the striatum, generally considered to be responsible for movement control, is also active during resting activity. Disturbances of the inhibitory striatal circuits might have therefore negative implications for both resting conditions and movement coordination.