MODIFIED VOLTAGE STDP AND CALCIUM SPIKES CAN EXPLAIN

ANTI-HEBBIAN PLASTICITY AT DISTAL DENDRITES

OF PYRAMIDAL NEURONS

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Phenomenological pair-based STDP rules (e.g. [1]) are commonly used to describe synaptic weight change with respect to time differences between pre- and post-synaptic spikes. However, pair-based models are unable to explain a variety of experimentally observed phenomena, including results of protocols involving triplets of spikes [2], and the switch from LTD to LTP for a post-pre spike pairing protocol as the frequency of presentation increases [3]. Voltage-based STDP [4] is a recently proposed model that is able to account for these findings, but not for the anti-Hebbian plasticity reported at distal dendrites of layer 5 pyramidal neurons when a pre-synaptic spike is paired with a post-synaptic burst [5].

By introducing calcium spike dynamics and using a more general form of voltage-based STDP model, we are able to reproduce the anti-Hebbian plasticity at the distal tuft. This approach is also able to account for how extracellular stimulation or dendritic current switches LTD to LTP in a pre-post protocol carried out on synapses at the distal dendrites of layer 5 pyramidal neurons [6]. The anti-Hebbian plasticity predicted by our extension of the voltage-based STDP model includes an LTP window for small time differences between the onset of the post-synaptic burst and the pre-synaptic spike, and an LTD window on either side. A specific experimental prediction of our model is that the magnitude of LTD for pre-post pairing will increase at higher frequencies whereas the magnitude of LTP post-pre pairing will decrease.

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COUPLING CHANGES ACROSS STRUCTURES AND FREQUENCIES IN THE HIPPOCAMPUS IN EPILEPSY

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Temporal lobe epilepsy is often accompanied by characteristic histological changes in the hippocampal formation. These changes should affect ongoing activity between epileptic events, which receives little attention and is often treated as 'control' activity. Signatures of these changes between epileptic events could contain crucial information about the activity state shaping the network prone to seizure generation.

We show that this ongoing acitvity under epileptic conditions is in fact different from ongoing activity under healthy conditions. In particular, we found a temporal shift in theta band activity between the medial entorhinal cortex and the dentate gyrus (DG) in the intra-hippocampal kainate mouse model in vivo. We suggest that this coupling change between structures is facilitated by cell loss in the hippocampus.

In addition, because cross-frequency coupling of gamma and theta is a prominent feature of the hippocampus, the shifted coupling of theta activity suggested that local gamma activity occurs at a different phase of theta. We confirmed this hypothesis by analysing the average power of gamma activity with respect to the theta wave in the DG. We show that high gamma activity (70-150 Hz) is in fact altered under epileptic conditions: the highest gamma power in healthy control mice occurs at the trough of a theta cycle in the DG whereas in comparable activity from epileptic mice, it occurs at the peak. As gamma activity is associated with fast inhibition, this finding may be associated with reduced inhibition in the DG.

LONG-RANGE CONNECTIVITY PROFILE OF L5B PYRAMIDAL NEURONS IMPLIES STRONG ROLE FOR HORIZONTAL PROJECTIONS

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In order to elucidate the role of local, cortical networks in information processing in the brain, a myriad of studies both experimental and theoretical have been conducted over the past decades, spanning all levels of investigation. Although the properties of local and inter-laminar synaptic connections have been investigated in detail, the question remains if this is sufficient to describe more generic properties of cortical networks. Several neuroanatomical studies (Hellwig 2000; Binzegger et al., 2004; Stepanyants et al., 2009; Voges et al. 2010) consistently suggested that an estimated 50-75% of the connections a neuron receives originate outside the local volume (radius: ~250μm). These connections have not been investigated in detail yet, but could have a strong impact on the local processing of information. Their high number together with potentially different connectivity patterns and synaptic properties might considerably change the view of how cortical networks process information. Here, we used photostimulation to map long-range horizontal projections to layer 5B pyramidal neurons in acute cortical slices. For lateral distances of 200-2000μm, we found intact projections and characterized their physiological properties as well as their layer of origin. The average amplitude of EPSPs slightly dropped with distance, while strong connections were still present over long distances. Short and long range connections showed an equally high synaptic reliability of 100% in most tested synapses, the same level of amplitude variability, and a high temporal precision of ~1ms. Indications for layer- and distance dependent differences in synaptic physiology are reported on especially for L5 and L6 projections. We conclude that long-distance horizontal connections could represent a substantial fraction of inputs to the local, cortical network. Secondly, although they showed a slight drop in amplitude with increasing distance, they contribute with reliable and precise inputs to single neurons in layer 5, thus impacting the local computation considerably.

PROJECTION PATTERNS ONTO DIFFERENT COMPARTMENTS OF LAYER V PYRAMIDAL NEURONS IN RAT NEOCORTEX

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Layer V pyramidal neurons constitute the major output population of the neocortex and show a complex morphology, especially the apical dendrite spanning all layers and terminating in a prominent tuft. During maturation, the apical dendrite and soma undergo a functional decoupling, resulting in a strong attenuation of EPSP's elicited by apical dendritic synapses. It has also been shown that apical dendrites can give rise to Ca^{2+}- and NMDA-spikes. While the projection patterns onto somata have been extensively examined, very little is known about the neurons projecting onto the apical dendrites, which may participate in regenerative potential generation.

Here we combined simultaneous apical dendritic and somatic in vitro patch-clamp recordings with presynaptic photo-stimulation via glutamate uncaging in rat somatosensory cortex. With these techniques, we examined the properties and layer-dependence of the projection patterns onto the two compartments of layer V neurons.

We detected EPSP's elicited by presynaptic neurons with horizontal distances of more than 1mm in acute slices and derived separate functional dendritic and somatic input maps. Thanks to simultaneous dendritic and somatic recordings, we were able to detect EPSP's which, due to the decoupling, were otherwise hardly detectable. These dendritic and somatic functional input maps showed considerable differences concerning the layers of the presynaptic neurons projecting onto the two compartments of layer V neurons. For the somata we found the reported inputs mainly originating from layers II/III, V and VI. By contrast, we found the supragranular layers to provide the predominant input onto the apical dendrites. These differences in input projection patterns may point to a compartment-specific integration of inputs from different cortical layers or neuronal sub-populations. These findings may help to further elucidate the role of the apical dendrites, in particular the mechanisms and neuronal populations involved in regenerative potential generation, in the input integration in layer V neurons.

LIQUID STATE PARTITIONING IN A NETWORK MODEL OF THE STRIATUM

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In reinforcement learning theories of the basal ganglia, dopamine is assumed to act as an error signal guiding the update of the values of such states during the learning process. Although it has been shown that a realistic dopaminergic error signal can drive the variant of RL known as temporal-difference learning [1] this study relied on a pre-defined partitioning of the environment into discrete states that were encoded as the firing rate of disjunct sets of neurons. A more likely scenario is that neurons are involved in the encoding of multiple different states through their spike patterns, and that an appropriate partitioning of an environment is learned on the basis of the actions leading to highest cumulative reward, such that patterns associated with the same actions are classified together. This is equivalent to a reduction in the effective number of states involved.

Here we present a purely inhibitory neuronal network model of the striatum that reproduces experimentally observed activity statistics [2] and allows an efficient state partitioning of a 2D environment, based on its transient high-dimensional dynamics [3] generated when stimulated with the spike coded position of the agent. The network can generalize over inputs with the same associated action and separate similar inputs with different associated actions, thus achieving liquid state partitioning.

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ASTROCYTES MODULATE THE BEHAVIOR OF NEURAL NETWORKS

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It is a common practice in experimental neuroscience to assess the statistical significance of spiking activity variations, measured from single or multiple neurons. For instance, in behavioral experiments, the probability of an increase in firing rate or correlation strength among a group of neurons is estimated under the assumption that an appropriately chosen null-hypothesis were true. If the probability for observing the experimental results under the null-hyppothesis is small, the results are deemed statistically significant and the neural activity is assumed to be functionally related to the task. Thus, it is also implicitly assumed that the statistically significant neural activity must have some effect on the network dynamics. However, this tacit inference is not warranted a priori. That is, the fact that the recorded neuronal activity is not a chance event does not necessarily imply that it will have an impact on local or downstream network activity, particularly when the network is not homogeneously random. Therefore, any strong, or even causal association to the behavior is not justified either.

We illustrate this largely ignored point by systematically analyzing the responses of 100 simulated spiking neuron networks, each composed of 10,000 neurons, to external stimulation. All networks had different topologies, however, the average connectivity parameters were kept constant. We measured the population activity and related it to network properties that characterize the way in which the stimulated neurons are embedded in their local environment. To estimate the embededness of neurons, we used known metrics from graph theory such as closeness centrality and k-shell decomposition. Our results indicate that the impact neuronal events have on local or downstream network dynamics strongly depends on the structural embeddedness of participating neurons. We discuss potential implications of our findings for the analysis of neuronal activity. We also point out additional hurdles that need to be overcome in extracting network function, which go beyond knowledge of the structure and dynamics.