Simulated relations of molecular, cellular, and neuronal network dynamics in a PFC network

SA Neymotin[1,2], Y Skolnick [1,3], RA McDougal[1,2], MM Hilscher[5,6], T Moulin[7], WW Lytton[1,4]

SUNY Downstate Medical Center[1], Yale University[2], CUNY Brooklyn College[3], Kings County Hospital, Brooklyn[4], Vienna University of Technology[5], Uppsala University[6] , Federal University of Rio de Janeiro[7]

Introduction

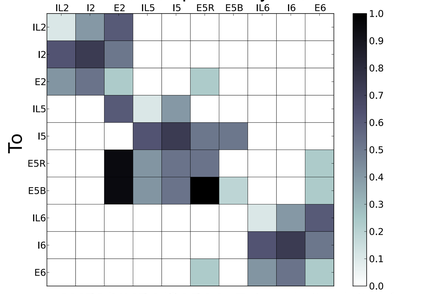
Multiscale modeling - time-scales and spatial-scales modeled: genetic regulation, chemical reactions, diffusion, ion-channel dynamics, action-potentials, learning, planning, decision-making. How does high-level function (and pathology) emerge from interactions across the disparate temporal and spatial scales?

Multiscale model of prefrontal cortex (PFC): Cognitive coordination is the brain's ability to dynamically select which information to utilize to generate appropriate behavioral responses. PFC plays a primary role in this coordination by its involvement in decision making and information representation in its working memory (WM) systems. WM depends on persistent activation of relevant neuronal ensembles and suppression of irrelevant neuronal ensembles. The dynamical discoordination hypothesis of schizophrenia maintains that relevant and irrelevant streams of information are not properly segregated. This pathology involves interactions across multiple spatial and temporal scales, visible at the behavioral (WM, decision making) and emerging from the genetic and molecular via alterations in signalling cascades involving multiple molecules (*i.e.*, dopamine dysfunction). The hyperpolarization-activated cation channel (HCN; with I_h current) facilitates short-term memory storage in the PFC via a signalling cascade involving protein kinases and intracellular Ca. We developed a multiscale computer model of PFC to investigate how the PFC maintains WM after receiving sensory stimuli. We used our model to make predictions about cognitive coordination deficits in schizophrenia.

Methods

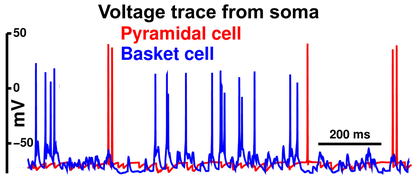
Network: 1552 conductance-based neurons arranged in Layer 2/3, 5, and 6. Layers consisted of populations of 5-compartment pyramidal neurons (E2 : layer 2/3 pyramidals) and two populations of interneurons (basket: I2 and low-threshold spiking: IL2).

Connection probability: From



Synapses: AMPA/NMDA/GABAA. External stimulation from other areas modeled as poisson inputs. Sensory stimuli presented as high-frequency inputs to select E5R cells (layer 5 pyramidal neurons).

Voltage trace from soma

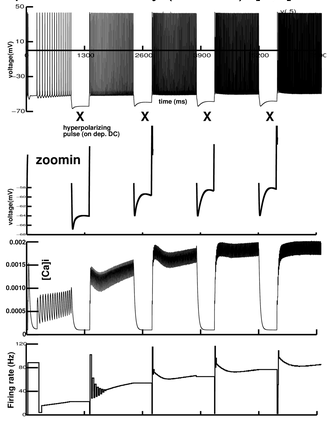


Intracellular dynamics: All cells contained Na and K channels for the generation of action potentials. Pyramidal cells contained long-lasting Ca channels, Ca accumulation mechanisms, and HCN channels that were modulated by a protein kinase. This kinase was further modulated by binding with Ca, as described previously [1]. LTS interneurons contained Ca, Ca-dependent K channels, and HCN channels, which were not Ca-dependent.

Results

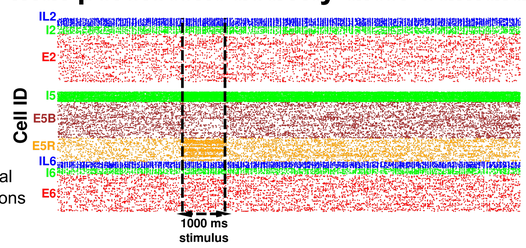
Cell level

PFC pyramidal cells with complex geometry and HCN channels display hyperpolarization-activated graded persistent activity (HAGPA) [1,2].

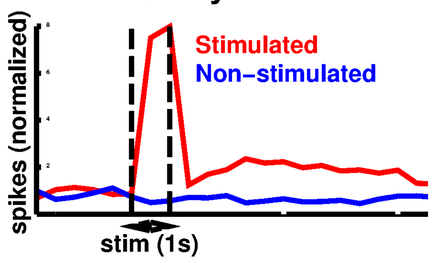


Network level

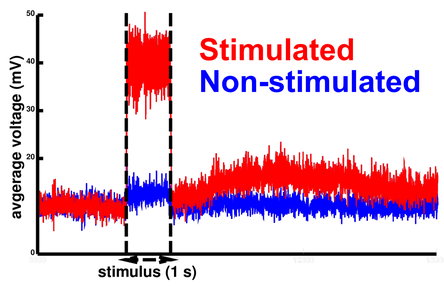
PFC network: layer 5 cell assembly with persistent activity after stimulus



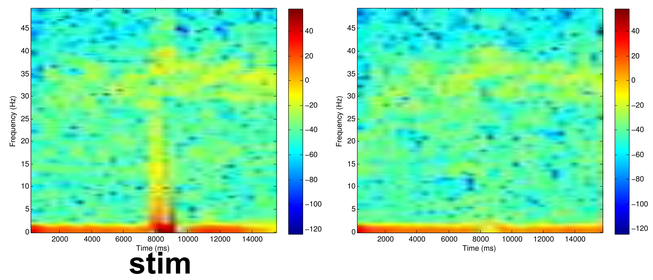
Persistent activity at multiunit level



Persistent activity at LFP level



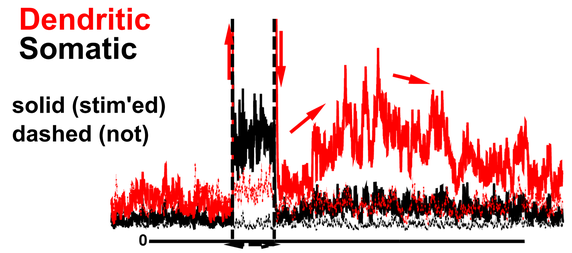
LFP shows post-stimulus increase in gamma (30-40 Hz) oscillations



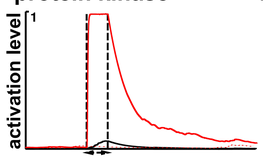
A closer look at intracellular dynamics:

calcium interactions with protein kinase and HCN required for HAGPA

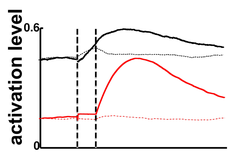
Integrated calcium signal shows accumulation



Ca influx activates protein kinase



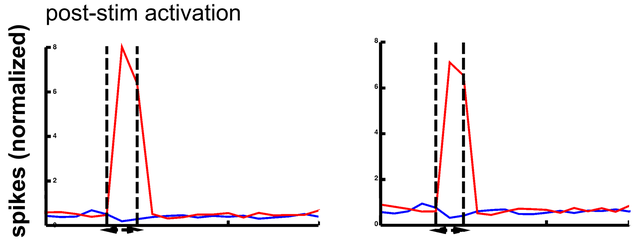
HCN ramping up via protein kinase and inhibition



Blocking different stages of the signalling cascade abolishes HAGPA

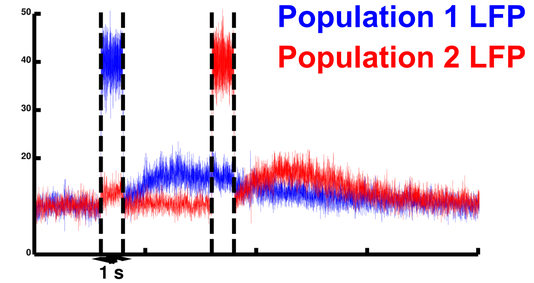
HCN block: short-term Ca accumulation without post-stim activation

L-type Ca channel block: no Ca accumulation



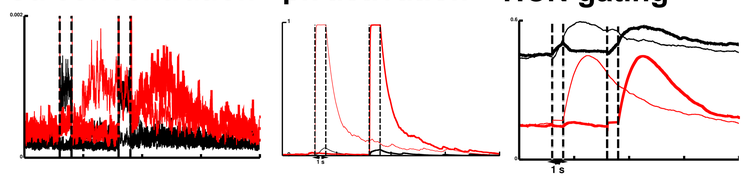
Further model development in elaborating the signalling cascade in PFC neurons and exploring the effects of attenuating or enhancing different stages in the signalling cascade (protein kinase activation, binding of protein kinase to HCN), and modelling diffusion/localization of different molecules, would enable more refined predictions as to the mechanisms of WM and its pathology in schizophrenia.

Network supports state-switching, while maintaining previously activated ensembles.



Switch-related intracellular dynamics

Ca concentration **pk activation** **HCN gating**



Conclusions:

1) We have developed a multiscale model of PFC with scales ranging from the intracellular to the neuronal network that exhibits features of WM including persistent activation and rapid state-switching.
2) In this model, Ca, protein kinase, and HCN interactions with network-generated excitation/inhibition contribute to the prolonged activation required for WM representation.
3) The PFC network exhibits WM-associated gamma rhythms, consistent with experimental evidence.

Predictions:

1) WM representation is history-dependent - a network can switch its focus but previously activated ensembles influence the ongoing representation.
2) In PFC, distinct ensembles compete dynamically by switching the levels of their activity and spike-time correlations.
3) Multiple ensembles switch relative activations dynamically at a time-scale consistent with the gamma cycle.
4) Dynamical selection of neuronal ensembles is degraded in the cognitive discoordination observed in schizophrenia due to alterations at the molecular and circuit level.

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References: [1] Hyperpolarization-activated graded persistent activity in the prefrontal cortex Winograd et. al, PNAS 2008.
[2] Predictive Features of Persistent Activity Emergence in Regular Spiking and Intrinsic Bursting Model Neurons. Sidiropoulou & Poirazi, PLoS Comp. Bio, 2012