Structured connectivity exploits NMDA-non-linearities to induce diverse responses in a PFC circuit

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Introduction

Working memory in the Prefrontal Cortex (PFC) involves the robust, yet flexible integration and maintenance of behaviorally relevant stimuli for a short-term period.

PFC neurons can be broadly selective for multiple stimuli/contexts and demonstrate rich temporal dynamics, yet network output contains a stable memoranda.

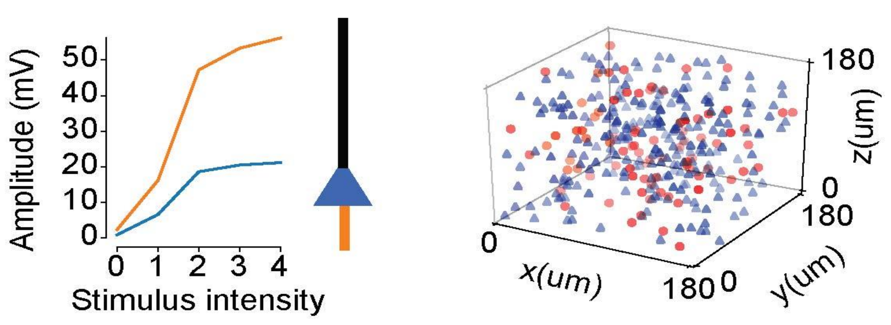
PFC neurons are characterized by highly non-linear dendritic responses and PFC networks by high recurrency.

Hypothesis:

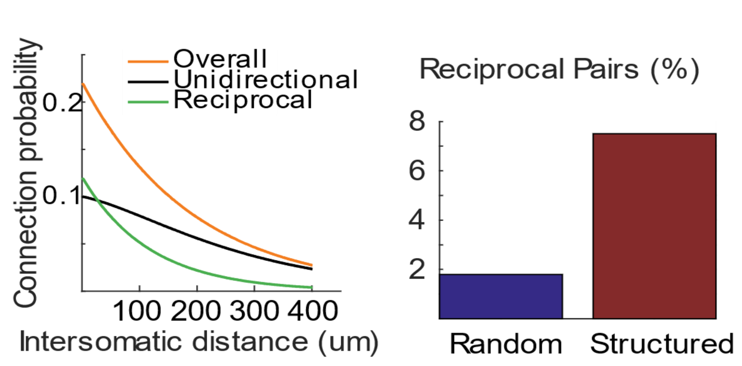
The highly flexible yet robust tuning in PFC can be mediated via a thresholding mechanism. This is created by synaptic facilitation, due to the NMDA nonlinear integration and emerges as a property of the PFC network connectivity profile.

Aim: *Characterize the role of **structured connectivity** and **dendritic non-linearities** in flexible working memory encoding in a PFC network.*

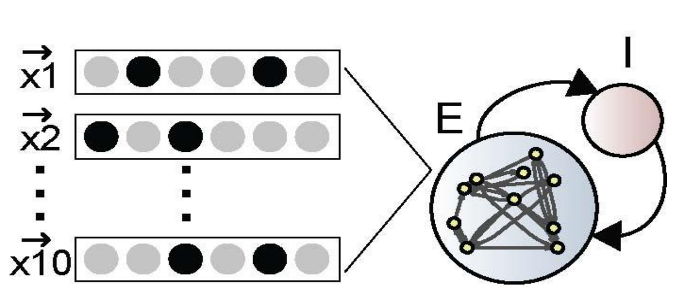
Methods



PFC model network consisted of 250 pyramidal (PCs) and 83 fast-spiking (FSs) inhibitory compartmental model neurons, that were morphologically simplified, yet biophysically detailed. Basal dendrites displayed non-linear synaptic responses. Excitatory (blue triangles) and inhibitory (red circles) connectivity profile was distance-dependent, based on experimental data.



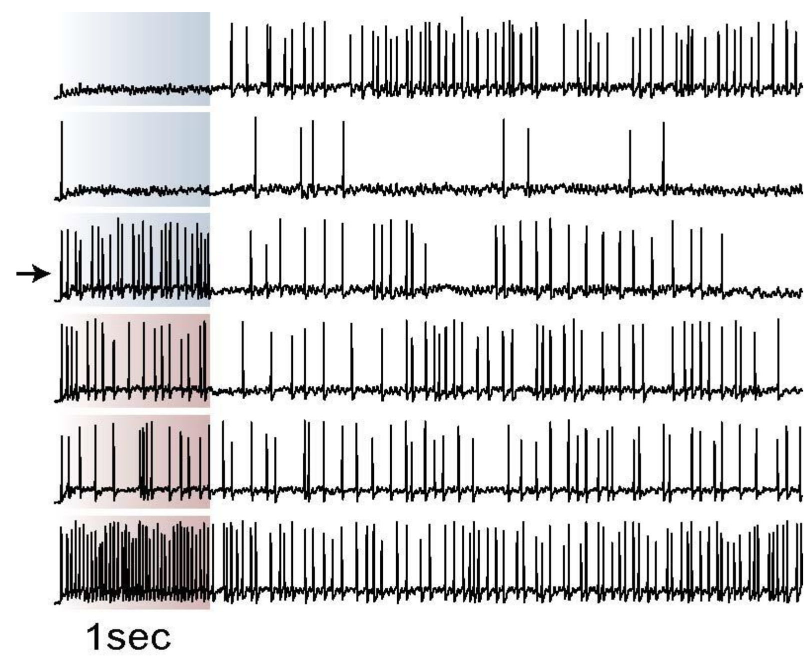
As a distinct feature of PFC, the network incorporates overrepresented reciprocally connected pairs. A random configuration was also simulated for comparison.



50 randomly selected PCs (n=10 trials) were stimulated for 1 sec, with uncorrelated Poisson trains. Network response is evaluated in the network state space, defined as the activity in a 50 ms time window.

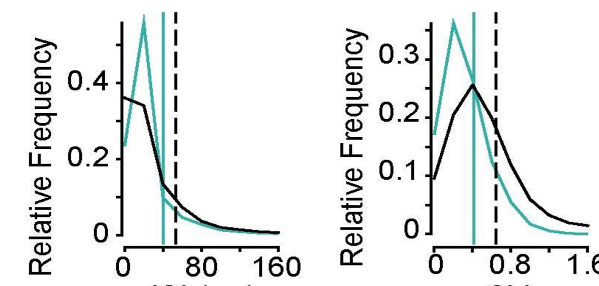
Results

Single–neuron dynamics

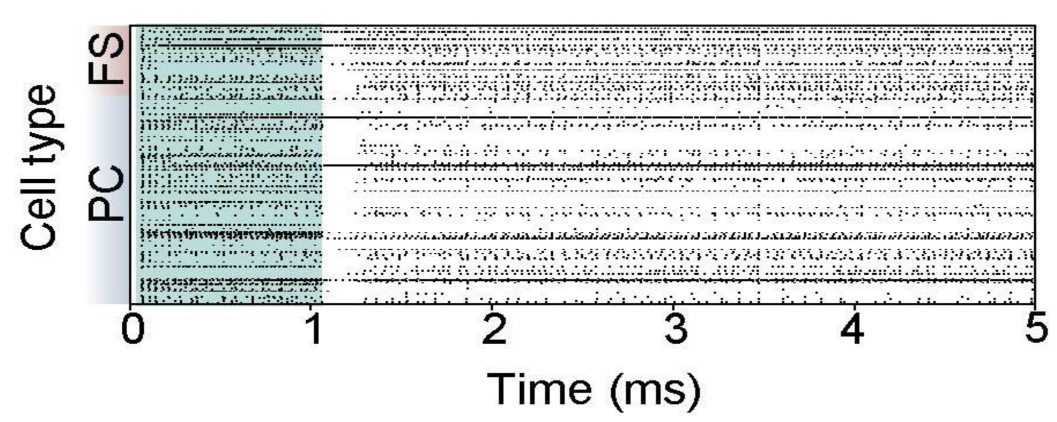


Exemplar voltage responses of PCs (top three) and FSs (bottom three) in a single trial. Shaded region indicates stimulus presentation (1sec). Arrow: PC that received stimulation.

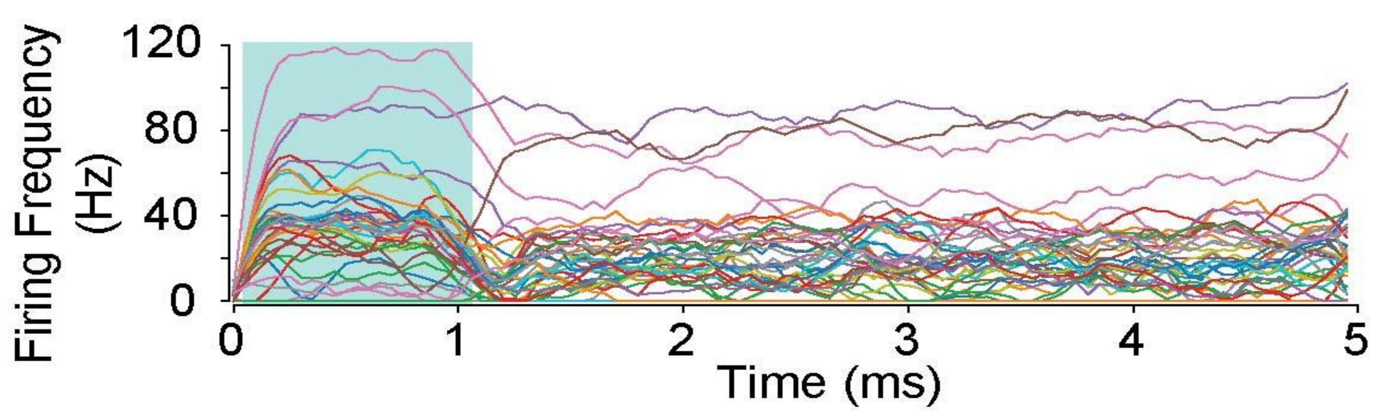
Pyramidal neurons display low firing frequencies and irregular spiking intervals.



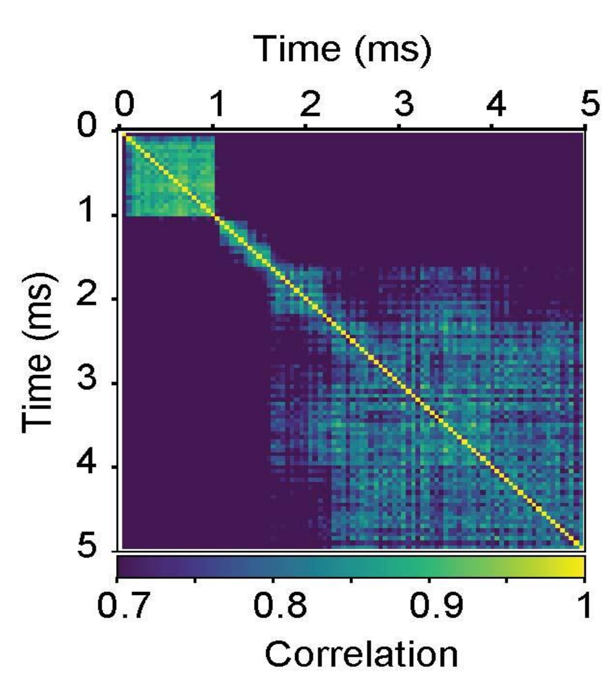
Network dynamics

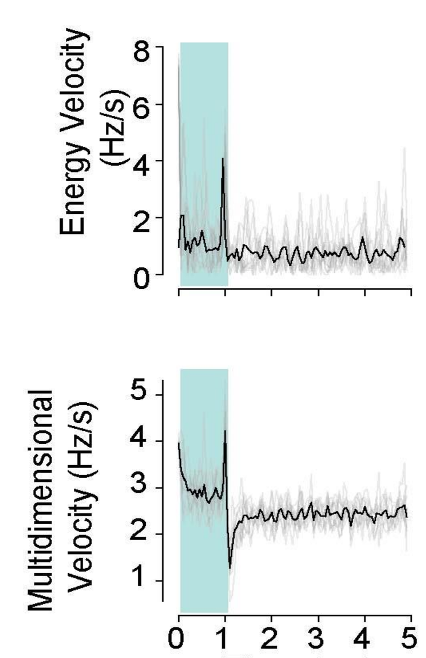


Network activity is sparse during the delay period.

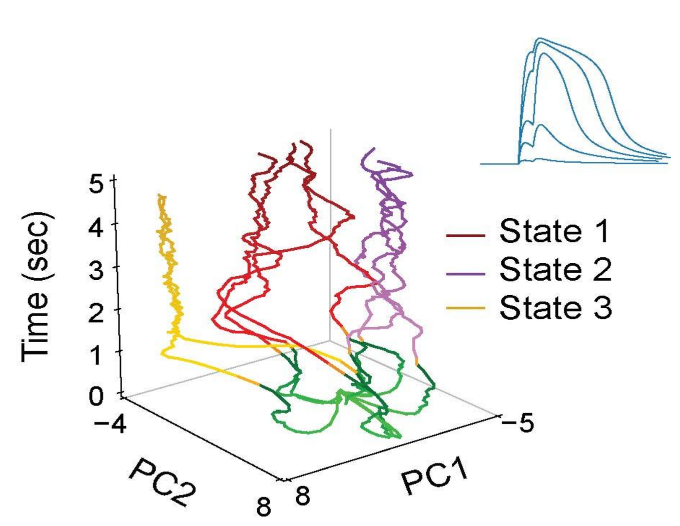


Individual pyramidal neurons respond irregularly. Activation of the network results in a dynamic temporal population response.

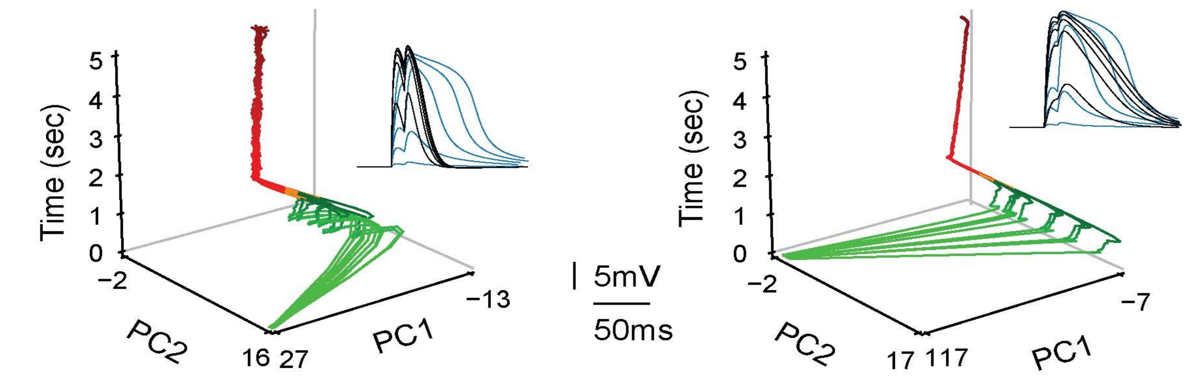




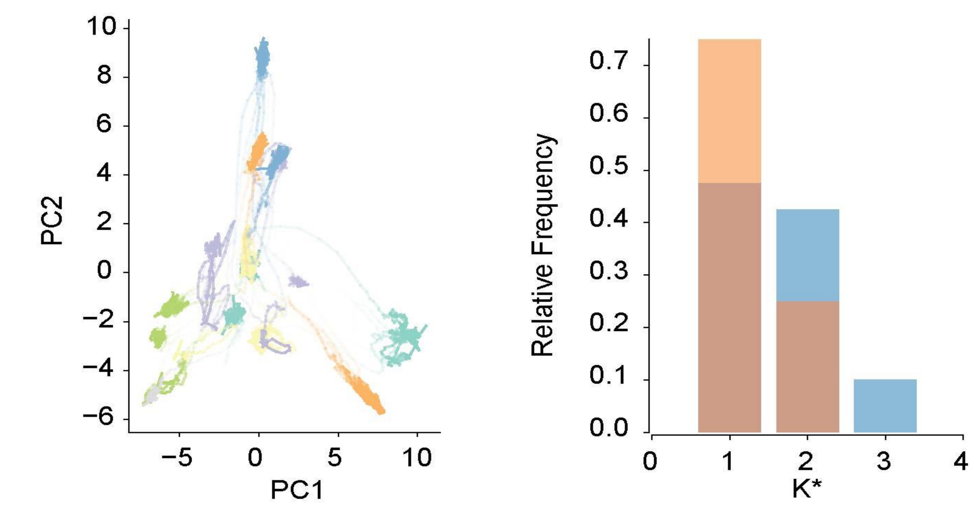
Late memory network state is decorrelated from the stimulus, reaching a low energy state.



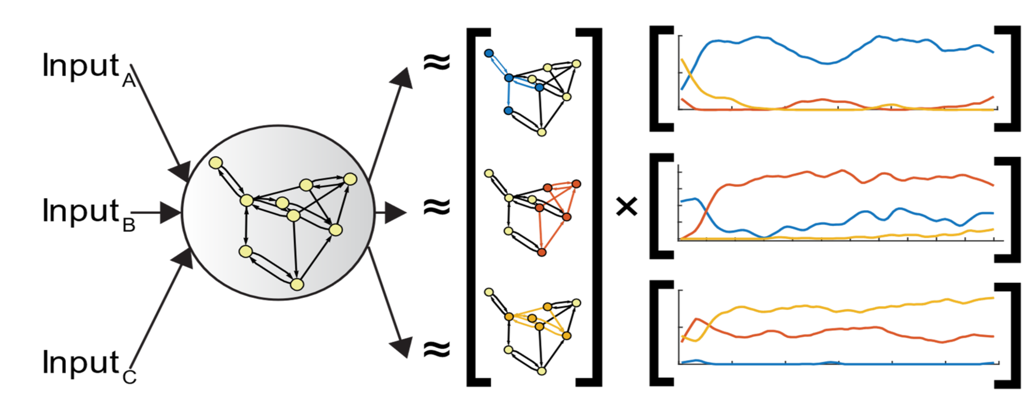
Network response in Principal Component space reveals a clear transition from the stimulus state, toward a different memory state.



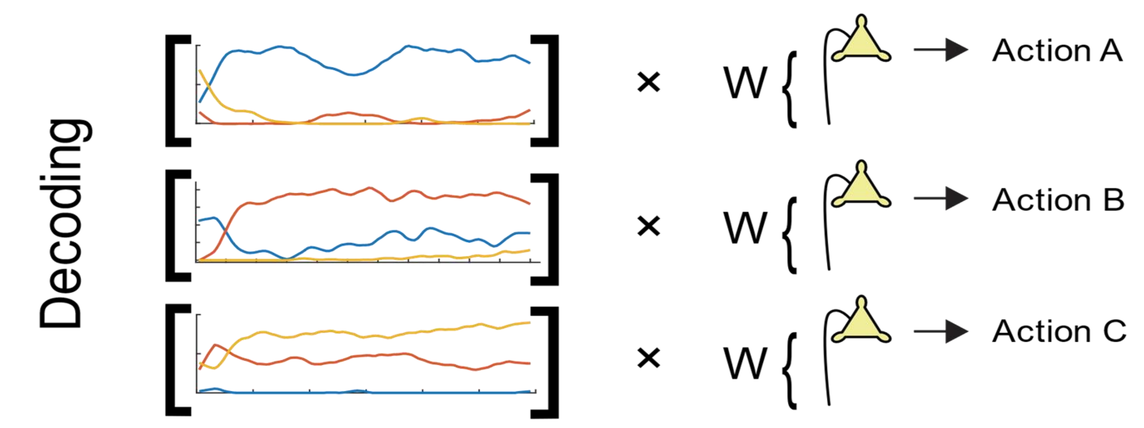
NMDA nonlinear synaptic integration is paramount for the generation of multiple network states.



Synaptic reconfiguration on dendrites is catalytic for shaping the memory space. Moreover, the NMDA nonlinearity is exploited better by the clustered structural connectivity.



The functional microcircuit: Network activity states can be approximately decomposed into distinct microcircuits and their activity (weight) vector. These functionally created microcircuits, are engaged due to specific input, respond solo or in combinations and in a relatively stable way over time.



Because the microcircuits are composed of different active neurons, this makes the total network activity quasi-orthogonal for the different memories, enabling downstream linear decoding.

Conclusions

This work provides a novel, validated compartmental model of the PFC network, that incorporates structured connectivity and dendritic nonlinearities. The model is used to probe the role of connectivity and dendritic non-linearities on working memory encoding.

We predict that structured connectivity is necessary for the encoding of multiple, robust memory representations on the same neuronal population. This feature is underlined by the activation of NMDA-dependent dendritic non-linearities and local clustering of connections.

References

Stokes, M.G., Kusunoki, M., Sigala, N., Nili, H., Gaffan, D., and Duncan, J. (2013). Dynamic coding for cognitive control in prefrontal cortex. Neuron 78, 364–375

Murray, J. D., Bernacchia, A., Roy, N. A., Constantinidis, C., Romo, R., & Wang, X.-J. (2017). Stable population coding for working memory coexists with heterogeneous neural dynamics in prefrontal cortex. Proceedings of the National Academy of Sciences, 114(2), 394–399. http://doi.org/10.1073/pnas.1619449114

Papoutsi, A., Sidiropoulou, K., & Poirazi, P. (2014). Dendritic Nonlinearities Reduce Network Size Requirements and Mediate ON and OFF States of Persistent Activity in a PFC Microcircuit Model. *PLoS Computational Biology*.

Perin, R., Berger, T. K., & Markram, H. (2011). A synaptic organizing principle for cortical neuronal groups. *Proceedings of the National Academy of Sciences of the United States of America*.

Acknowledgments

This project has received funding from the ERC starting Grant "dEMORY: Dissecting the role of dendrites in memory" and the Hellenic Foundation for Research and Innovation (HFRI) and the General Secretariat for Research and Technology (GSRT), under grant agreement No 1357.