Network models predict that pyramidal neuron hyperexcitability and synapse loss in the dlPFC lead to age-related spatial working memory impairment in rhesus monkeys

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INTRODUCTION

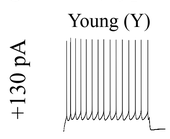
Using computational models, we studied how age-related changes in the properties of individual pyramidal neurons (PNs) in the layer 3 of area 46 (dlPFC), in the rhesus monkey, relate with the impairment of their spatial working memory (SWM).

1.- Behavioral studies: cognitive performance in SWM tasks declines with aging.
2.- *In vitro* & *in vivo* studies: PNs undergo structural & electrophysiological changes with aging.

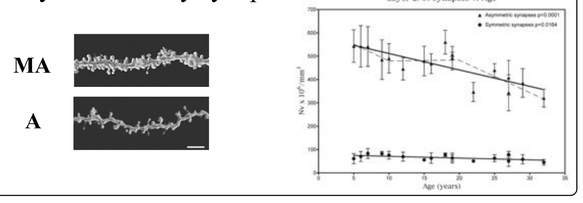
Spatial information is encoded in the persistent firing activity of PNs in the dlPFC during a SWM task. Thus, perturbations of their properties in aging are likely to be a significant determinant of declines in SWM.

SINGLE PN AGING EFFECTS — *MODELING* → **BEHAVIOR**

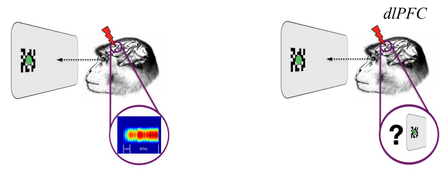
1.- *In vitro* electrophysiology: increased action potential (AP) firing rates[1] (hyperexcitability).



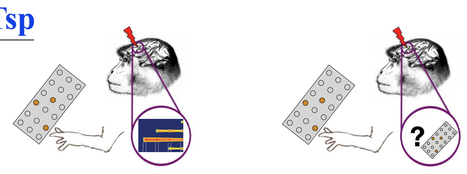
2.- Electron microscopy: 10 % (MA) - 30% (A) reduction in excitatory & inhibitory synapses[2].



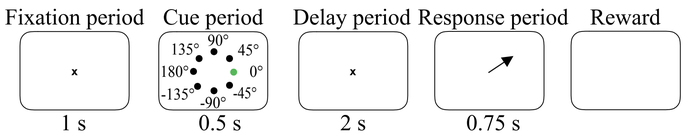
DRT



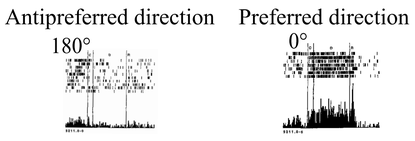
DRSTsp



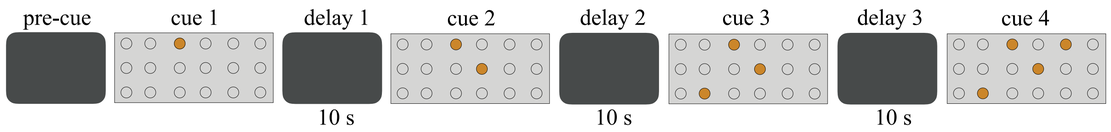
Delayed Response Task (**DRT**) / Oculomotor Task



Spatial selectivity of PNs



Delayed Recognition Span Task in the spatial condition (**DRSTsp**)



MODELS

DRT model[3]: Bump attractor dynamics with firing-rate neurons. 640 excitatory (E) & 160 inhibitory (I) neurons.

$$\tau_E \frac{dr_E^i}{dt} = -r_E^i + f_E(I_E^i) + \sigma_E \xi_E^i(t)$$

$$I_E^i(t) = I_{Ea}^i(t) + I_{En}^i(t) + I_{Eg}^i(t) + I_{0E} + I_{stim}^i$$

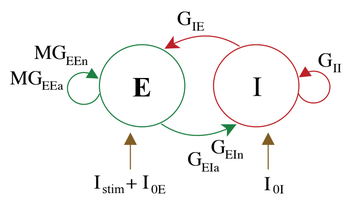
$$\tau_a \frac{dI_{Ea}^i}{dt} = -I_{Ea}^i + \sum_{i=1}^{N_E} G_{EEa} M_{ji} r_E^i$$

$$\tau_n \frac{dI_{En}^i}{dt} = -I_{En}^i + \sum_{i=1}^{N_E} G_{EEn} M_{ji} r_E^i$$

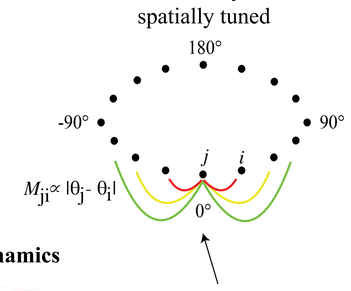
$$\tau_g \frac{dI_{Eg}^i}{dt} = -I_{Eg}^i + G_{IE} \bar{r}_I$$

$$f(I) = \begin{cases} 0 & I \le 0 \\ \nu_c \left(\frac{I}{I_c}\right)^2 & 0 < I < I_c \\ 2\nu_c \sqrt{\frac{I}{I_c} - \frac{3}{4}} & I_c \le I \end{cases}$$

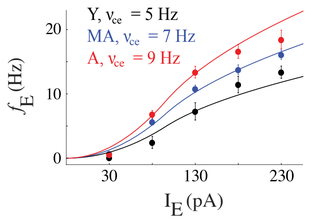
Network



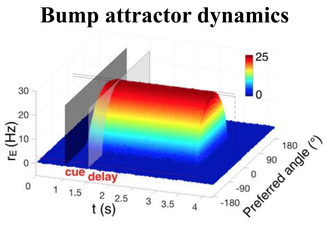
M connectivity matrix spatially tuned



***f*-I curve**: single neuron firing rate.



Bump attractor dynamics



Simulations:

The space-filling Latin Hypercube Sampling (LHS) design[4] was used to identify 4200 points across the parameter space of $G_{EE,A}$, $G_{EE,N}$, G_{IE} $G_{IE,A}$, $G_{IE,N}$, & G_{II}. The bump attractor network was simulated at each of these points, in several conditions to find points in the LHS that maintained tuned persistent activitytuned to the stimulus location (TPA-S) during the delay.

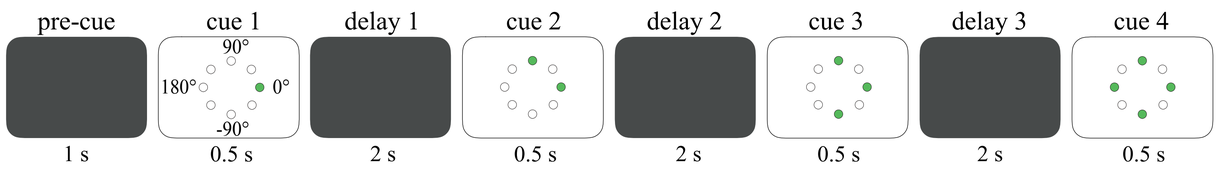
DRSTsp model: modeling memory retention in the DRSTsp based on the DRT setup, plus short-term synaptic facilitation.

utilization parameter

Facilitated excitatory connections among E neurons[5]:

$$\tau_a \frac{dI_{Ea}^j}{dt} = -I_{Ea}^j + \sum_{i=1}^{N_E} G_{EEa} M_{ji} \underline{u^i} r_E^i \qquad \tau_n \frac{dI_{En}^j}{dt} = -I_{En}^j + \sum_{i=1}^{N_E} G_{EEn} M_{ji} \underline{u^i} r_E^i$$

$$\tau_f \frac{du}{dt} = -(u - U) + \tau_f U r_E (1 - u)$$

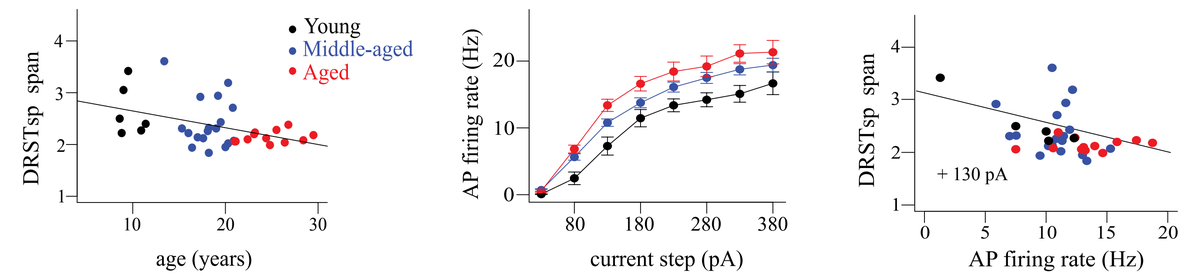


Modeling aging conditions:

1.- Hyperexcitability: modeled by increasing the parameter ν_{ce} in the *f*-I curve.
2.- Loss of the E and I synaptic inputs: modeled by perturbing the synaptic weights.
- DRT: a 10% (MA condition) - 30% (A condition) decrease in $G_{EE,A}$, $G_{EE,N}$, and G_{IE}.
- DRSTsp: semi-continuous decrease in $G_{EE,A}$, $G_{EE,N}$, and G_{IE} .

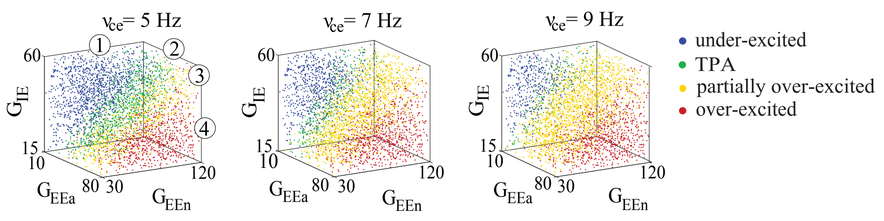
RESULTS

1 (*empirical*) Rhesus monkeys show DRSTsp impairment and increased AP firing rates of dlPFC PNs with aging, and a negative correlation of the DRSTsp span with the AP firing rates.

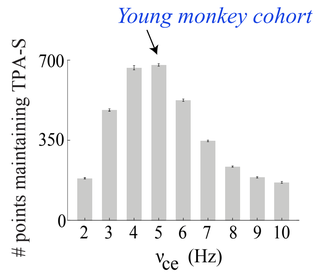


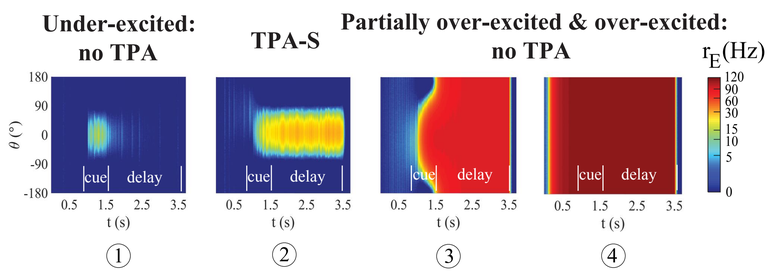
2 The DRT model shows an optimal level of PN excitability to maximize successful performance. In successful networks, lower excitatory synaptic weights and higher inhibitory weights partially compensated for increased PN excitability.

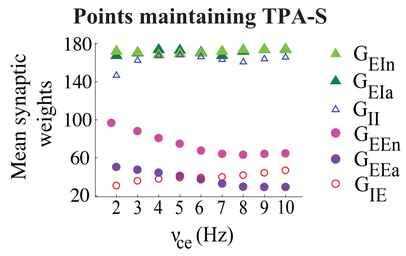
Pyramidal neuron excitability increases →



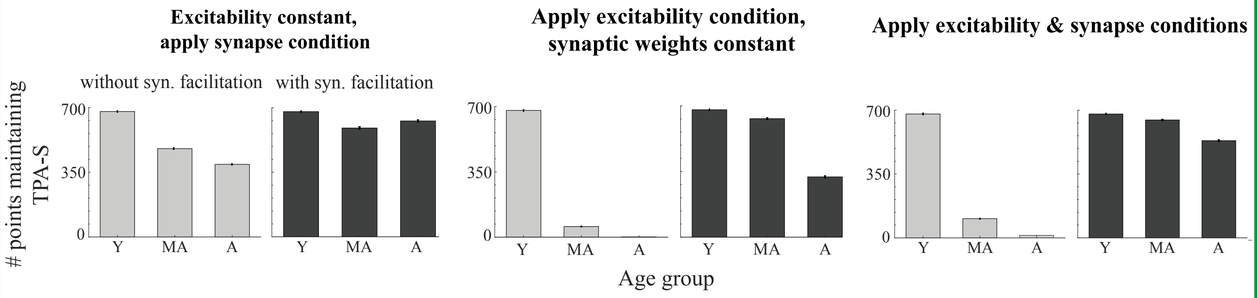
Young monkey cohort





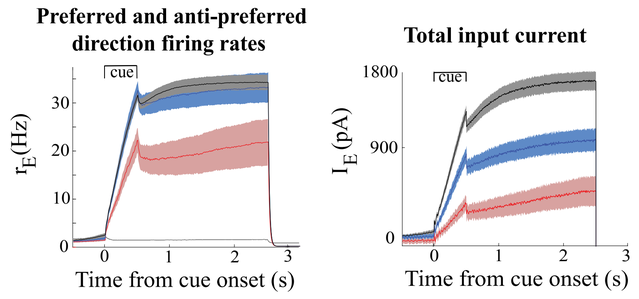


Young monkey cohort:



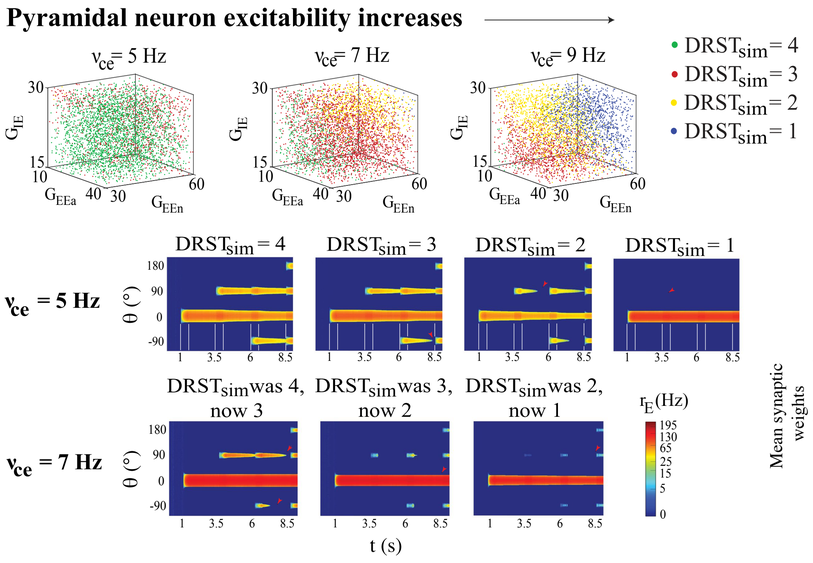
3 As seen in vivo, successful DRT networks have lower firing rates[6] and lower synaptic input currents in aged vs. young models:

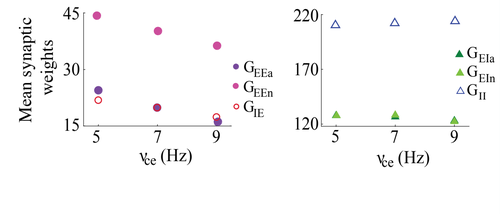
- Young preferred
- Middle-aged preferred
- Aged preferred
- Anti-preferred



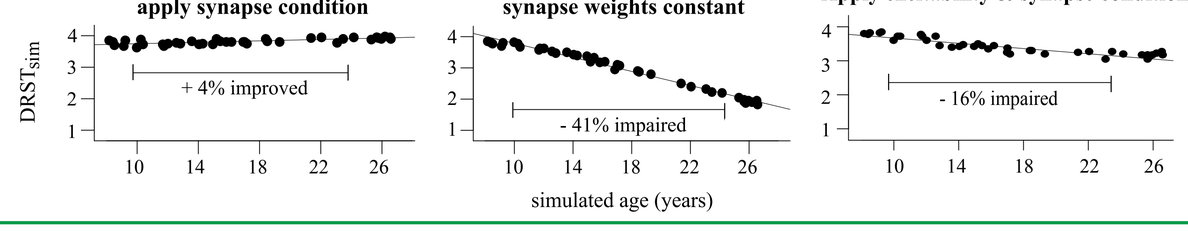
4 PN hyperexcitability leads to reduced memory capacity in simulated DRSTsp networks. In successful networks, lower excitatory & inhibitory weights partially compensated for increased PN excitability.

Pyramidal neuron excitability increases →





5 "Aging" the DRSTsp model networks led to working memory impairment as observed empirically.



CONCLUSIONS

Our models predict that:

1. PN hyperexcitability and synapse loss in the dlPFC together may be sufficient to explain empirically observed levels of SWM impairment as rhesus monkeys age.
2. SWM is impaired significantly by PN hyperexcitability alone, but not by the loss of excitatory and inhibitory synapses (which correlates with empirical findings[7]).
3. Hyperexcitability in individual PNs with aging is compensated within the network by lower total synaptic input current to each neuron, uniting our *in vitro* observations with *in vivo* data.
4. Persistent activity and synaptic facilitation are both essential for working memory tasks involving multiple spatial cues, and synaptic facilitation plays an essential compensatory role in aging.

References

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