

# Serotonin regulates working memory function non-monotonically in a computational network model: implications for schizophrenia

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Rita Almeida

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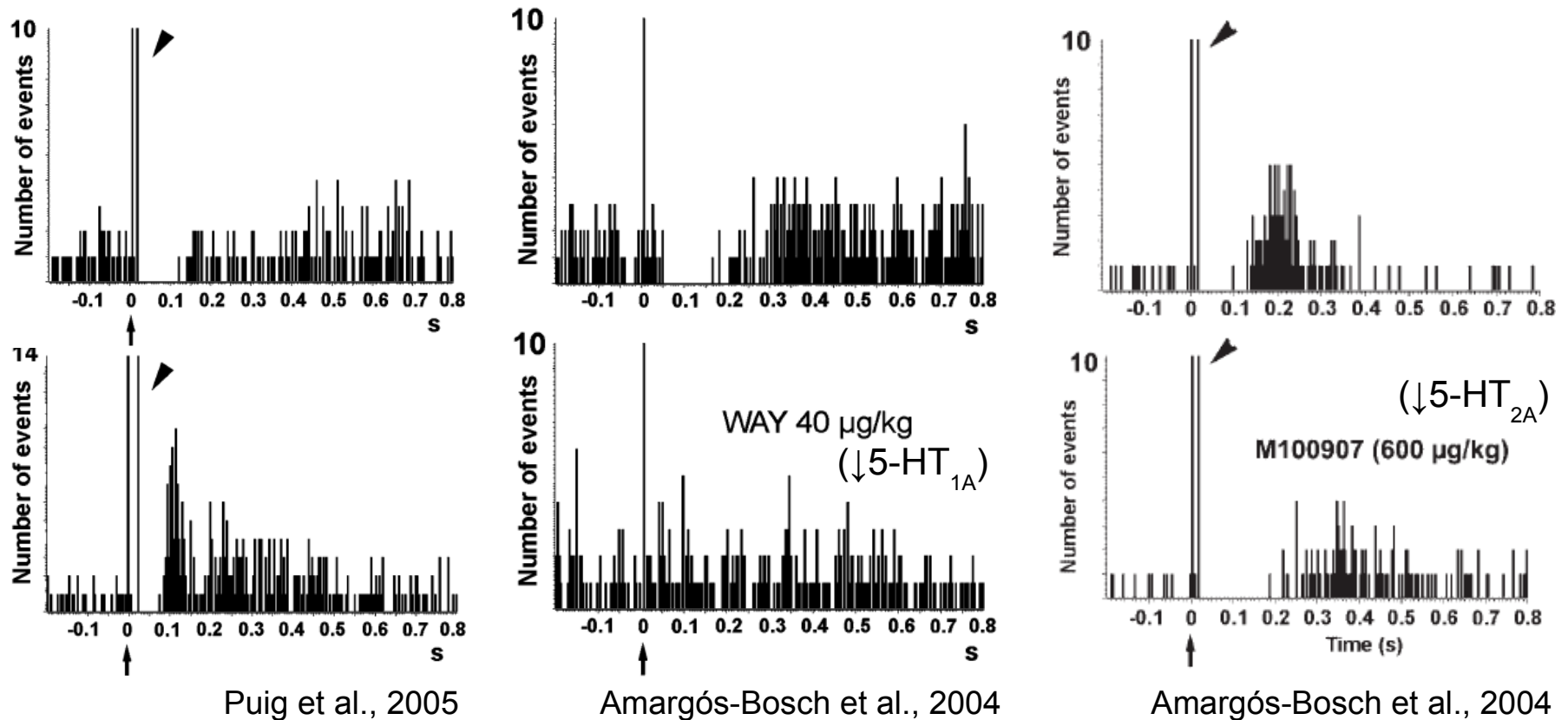
Francesc Artigas

Albert Compte

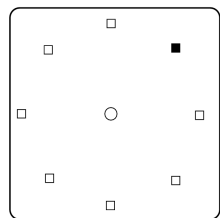
IDIBAPS, Barcelona, Spain



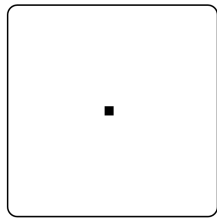
# DRN stimulation causes PFC activity suppression *in vivo*



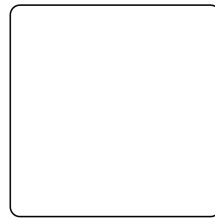
# Spatial working memory: persistent activity in PFC



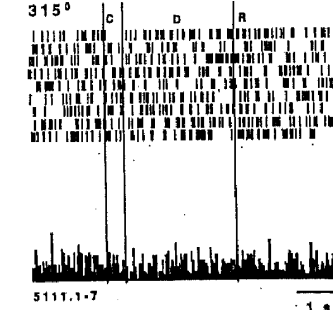
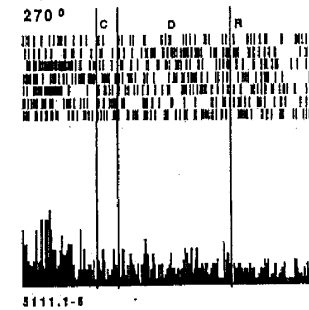
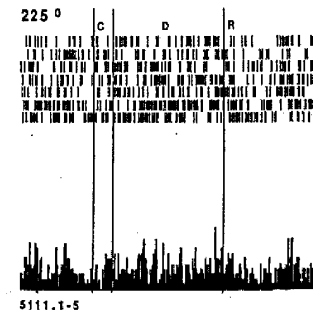
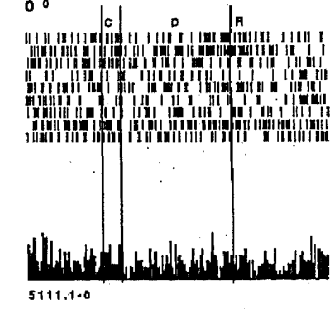
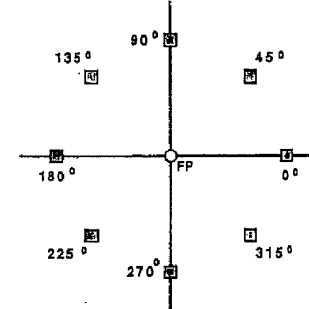
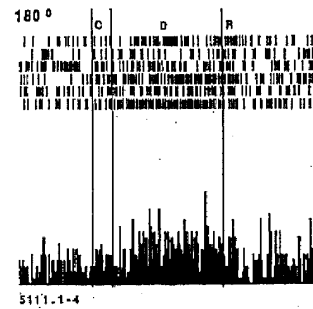
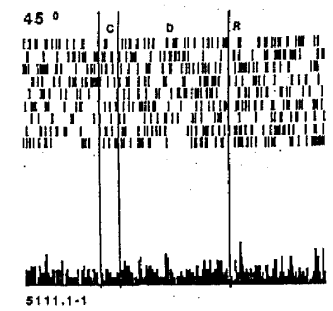
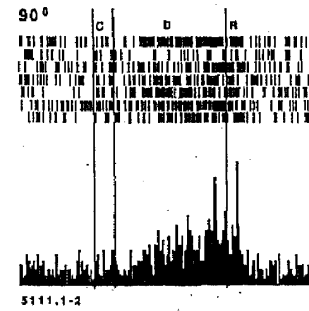
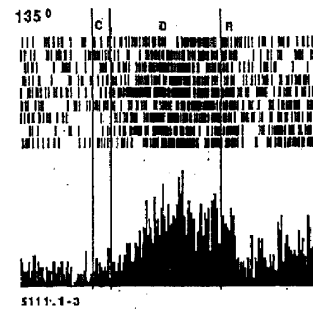
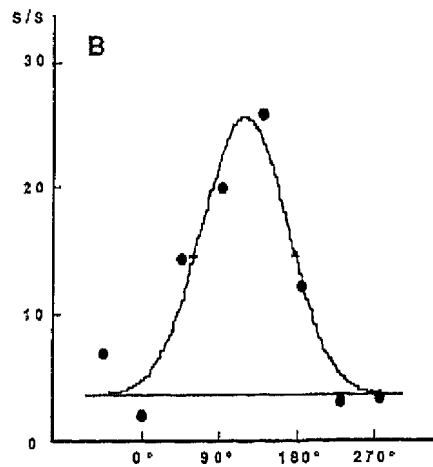
Stimulus



Delay



Response

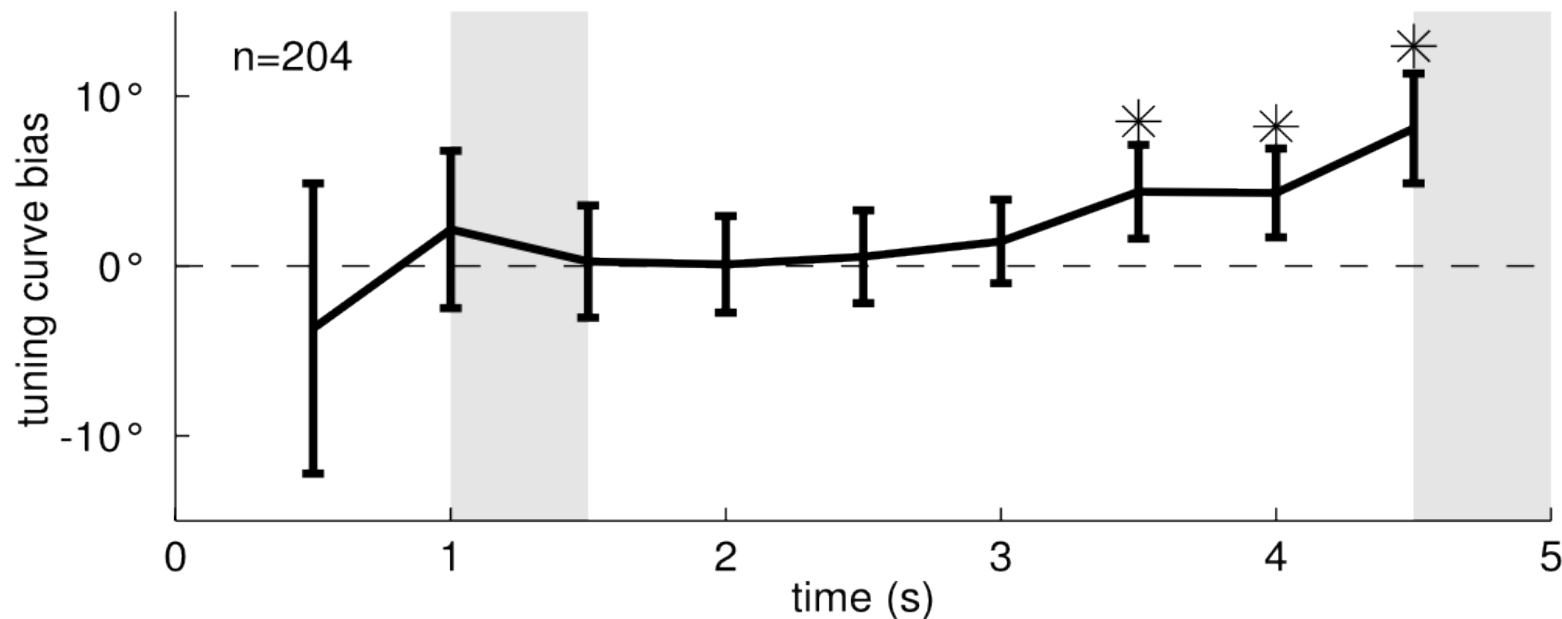
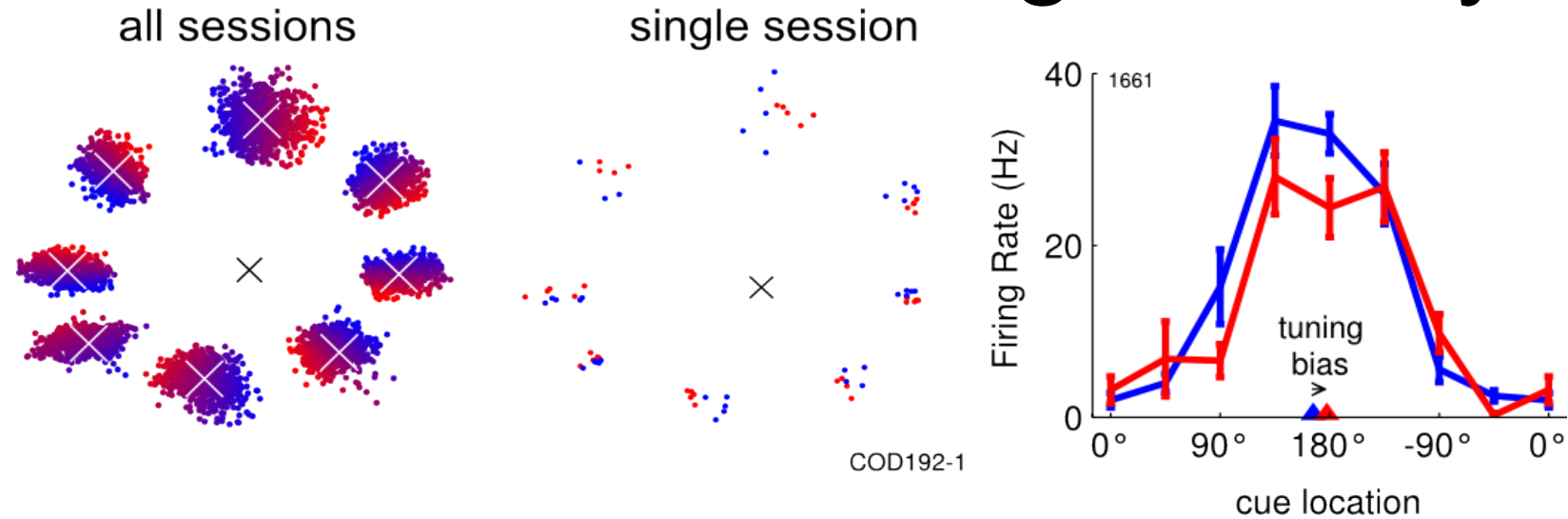


50 s/s

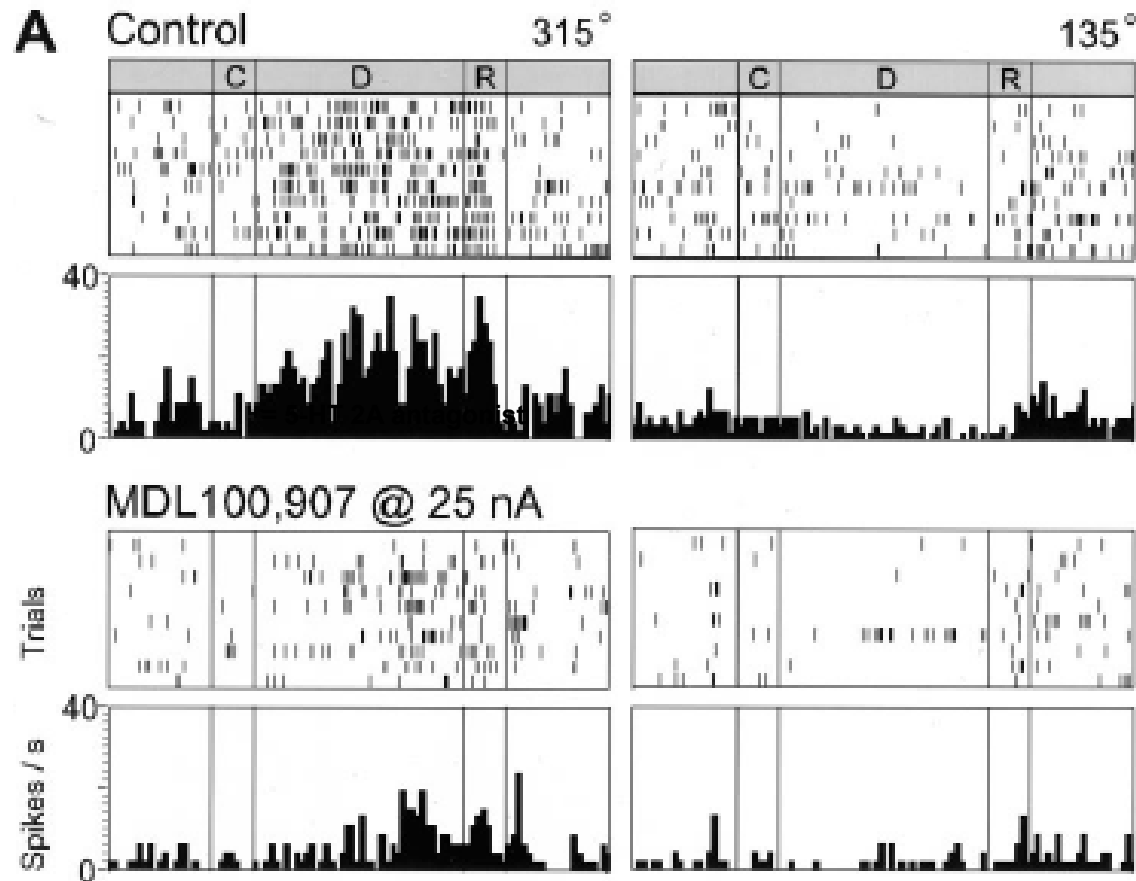
1 s

(Funahashi and Goldman-Rakic, J Neurophysiol 1989)

# Neural evidence of continuous attractors for working memory



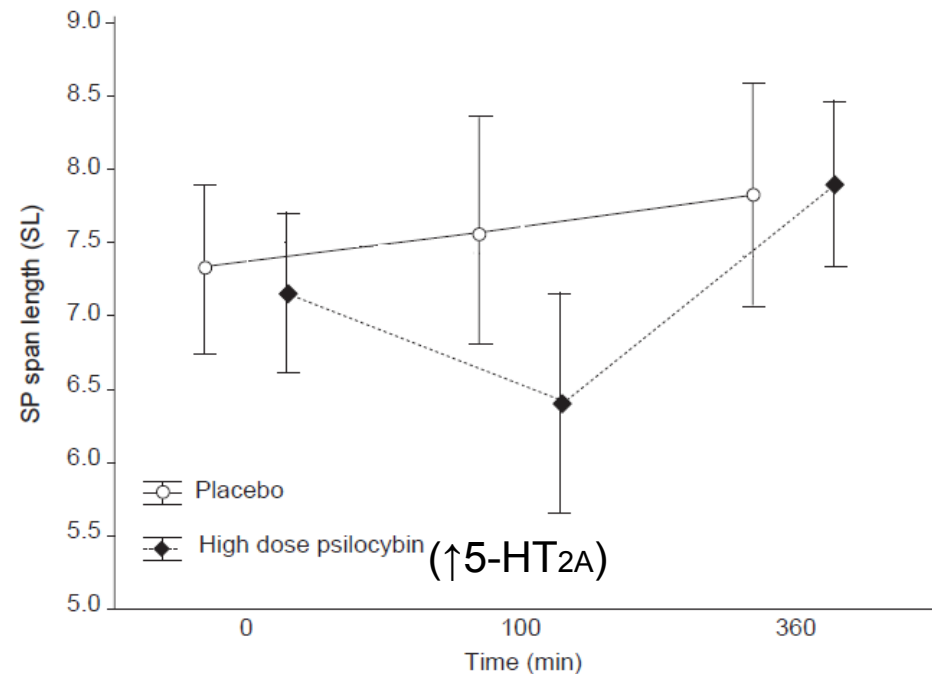
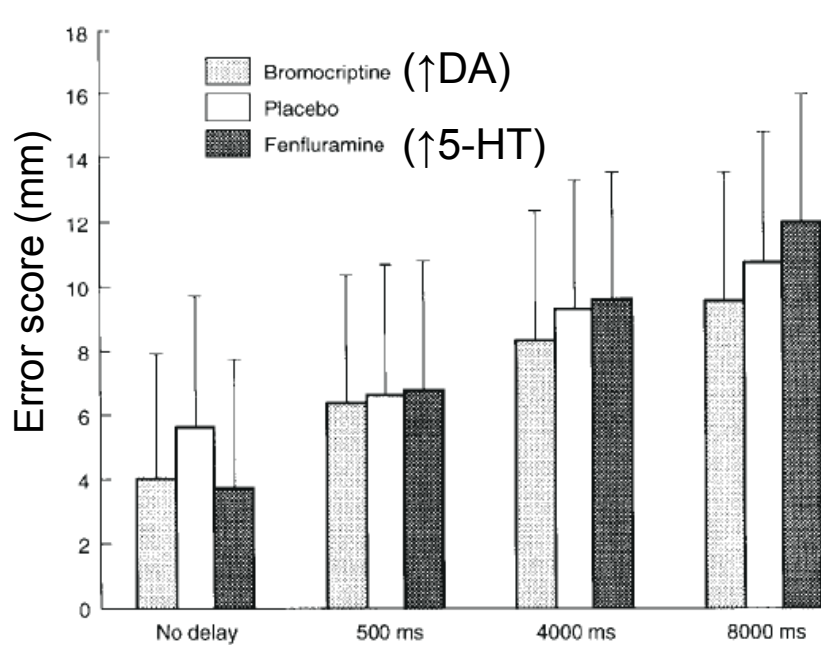
# Iontophoretic application of 5-HT<sub>2A</sub> drugs affects neural tuning in PFC



(Williams et al. 2002)

# Serotonin and spatial working memory performance...

- 5-HT drugs affect spatial working memory (Luciana et al. 1998; Wittmann et al. 2007)



- 5-HT drugs do not affect WM (Park et al. 1994; Luciana et al. 2001)

# Serotonin, WM and schizophrenia

- Spatial WM is affected in SZ patients (Park and Holzman 1992), with a genetic component (Glahn et al 2003)
- Cognitive symptoms are considered a core deficit of SZ (Barch and Ceaser 2012)
- Some antipsychotics target primarily 5-HT receptors
- Some antipsychotic treatments induce neurocognitive improvements (Keefe et al. 2007)
- 5-HT drugs are being investigated as possible cognitive enhancers in SZ (Terry Jr et al. 2008)

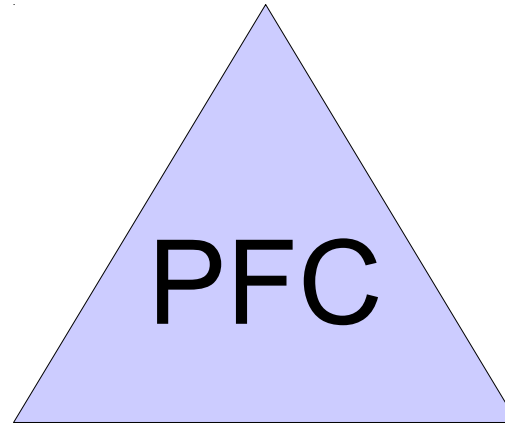
**5-HT and persistent activity**  
(Williams et al. 2002)

**5-HT and sWM behavior?**  
(Luciana et al. 1997, 2001;  
Wittmann et al. 2007)

**Serotonergic  
transmission**

**Atypical antipsychotics  
target 5-HTRs**

**Hallucinogens acting  
on 5-HTRs mimic SZ**  
(Vollenweider et al.  
1998)



**Spatial working  
memory**

**Schizophrenia**

**Impaired sWM in SZ patients** (Park and Holzman 1992)  
**Antipsychotic treatments affect sWM** (Reilly et al. 2006)  
**Abnormal PFC activation for sWM in SZ** (Carter et al. 1998,  
Manoach et al. 1999, Lee et al. 2008,...)



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1998)

**Computational network  
model of PFC**

**Spatial working  
memory**

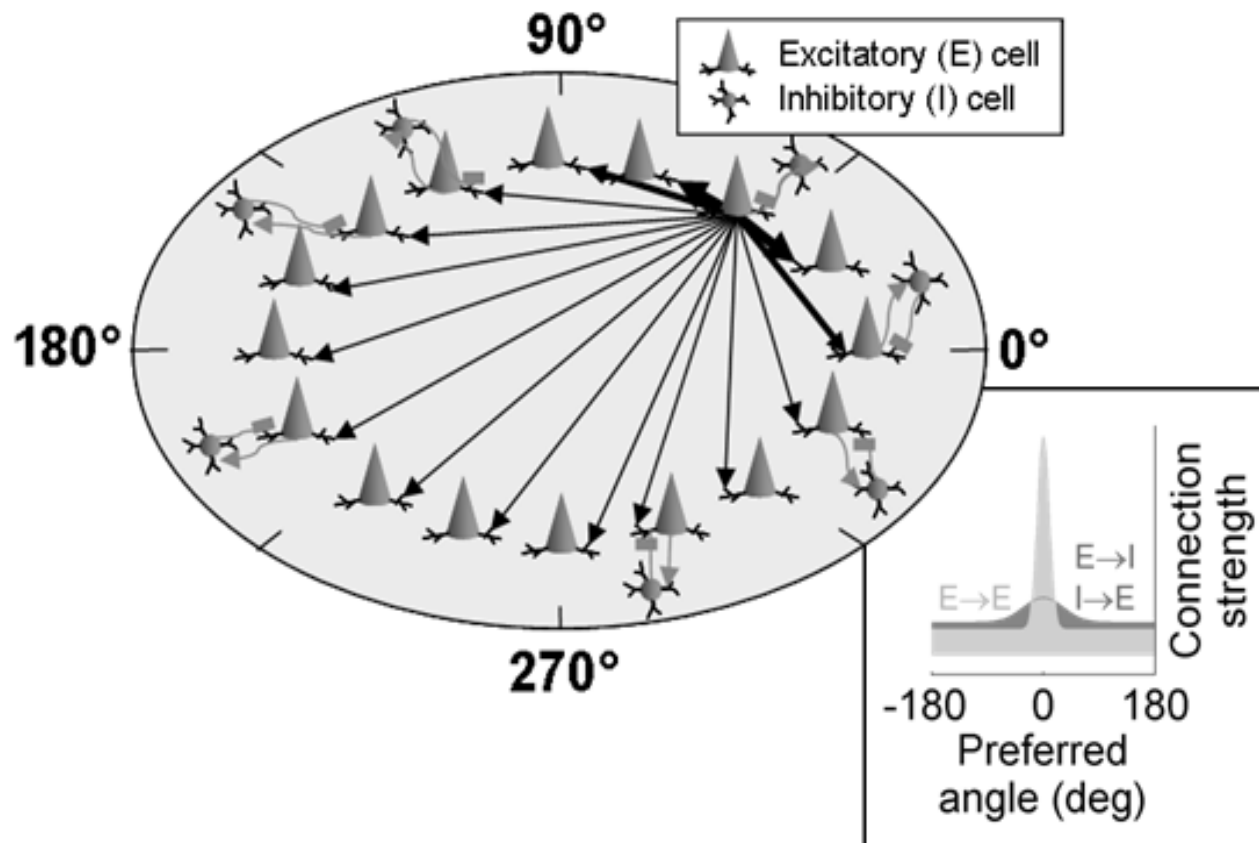
**Schizophrenia**

**Impaired sWM in SZ patients** (Park and Holzman 1992)

**Antipsychotic treatments affect sWM** (Reilly et al. 2006)

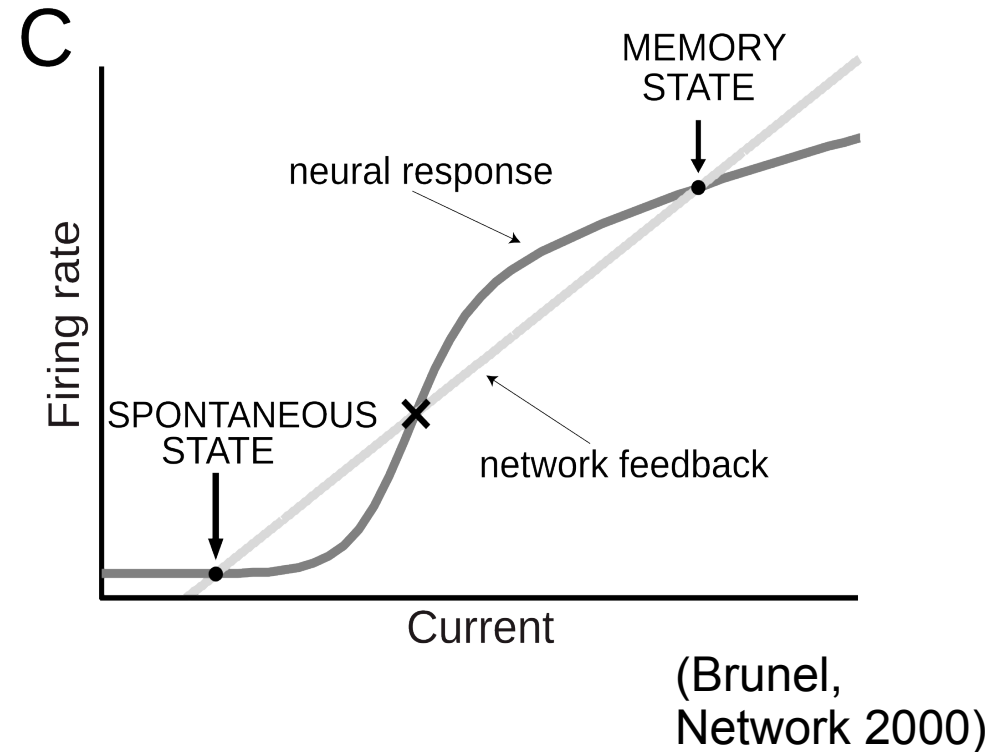
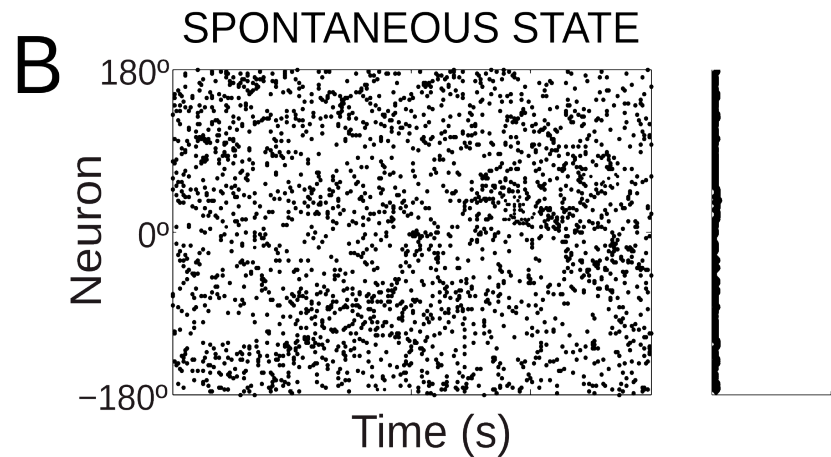
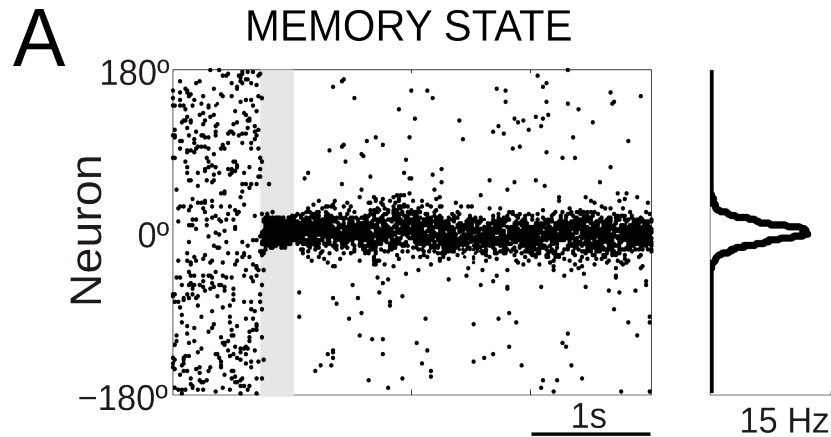
**Abnormal PFC activation for sWM in SZ** (Carter et al. 1998,  
Manoach et al. 1999, Lee et al. 2008,...)

# Ring model for *spatial* working memory



(Compte *et al.* Cereb Cortex 2000)

# Local circuit mechanisms

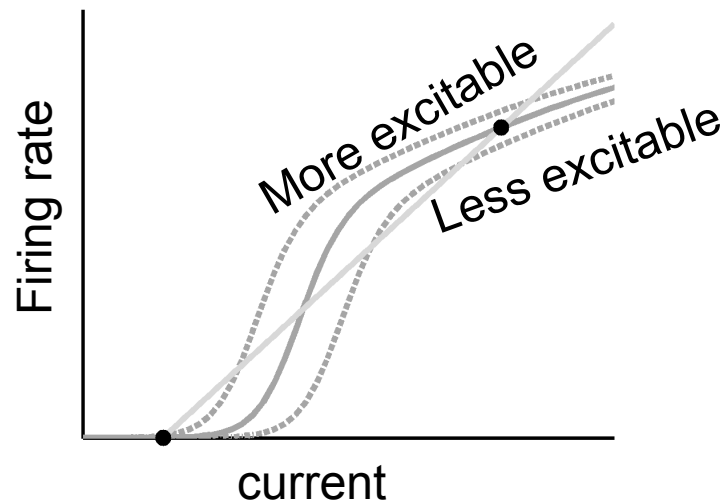


- Strong focal excitation → persistence
- Strong non-selective inhibition → tuning

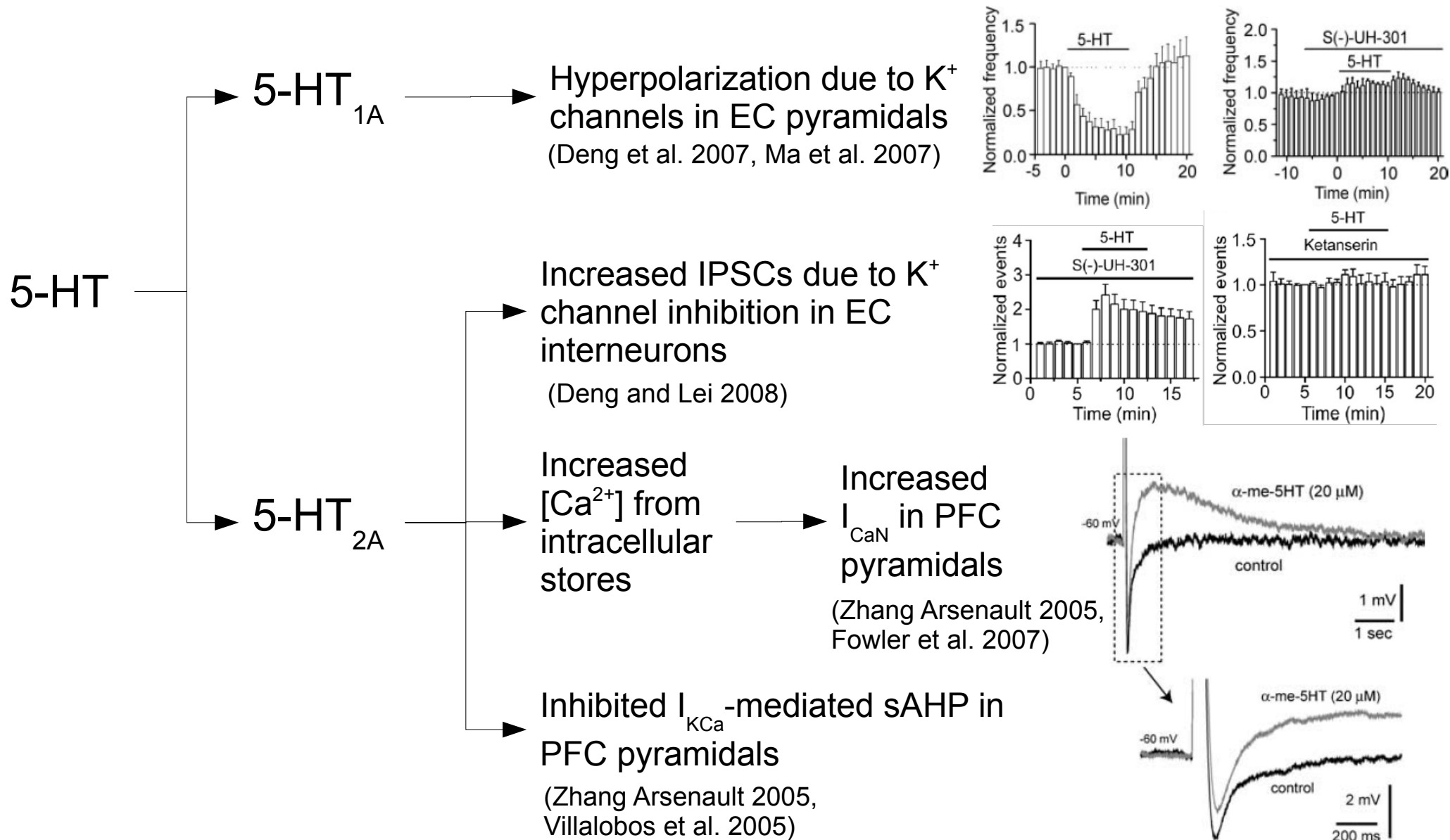
(Compte et al.,  
Cereb Cortex 2000)

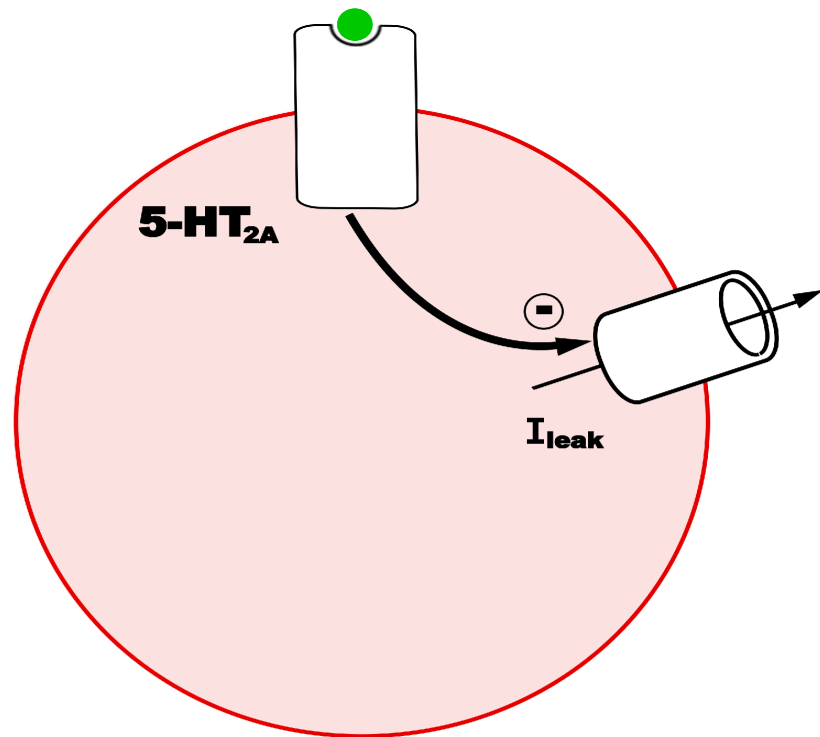
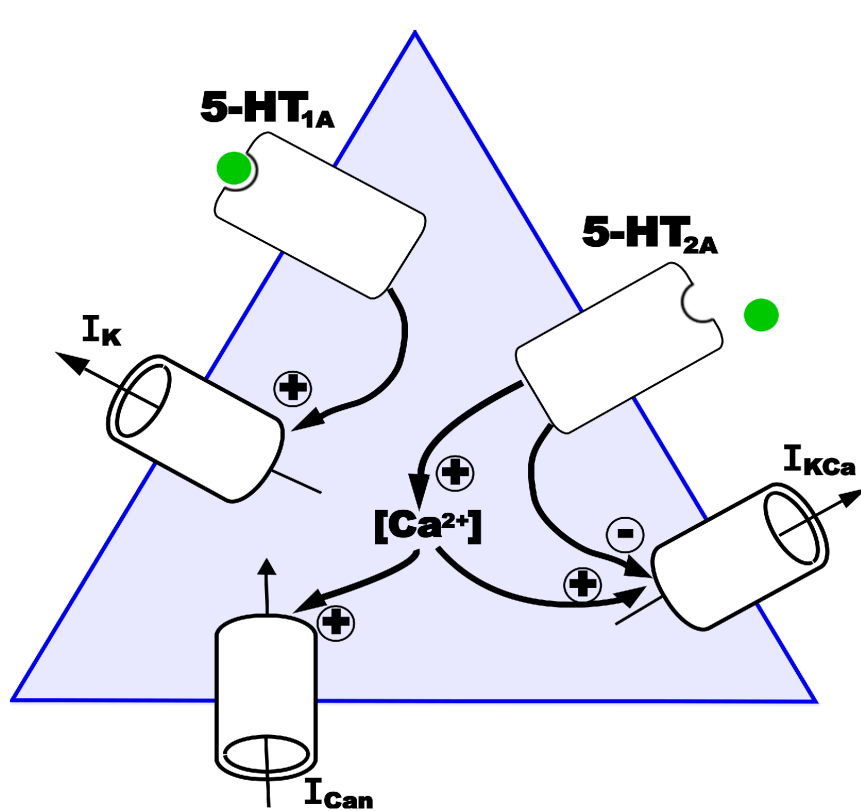
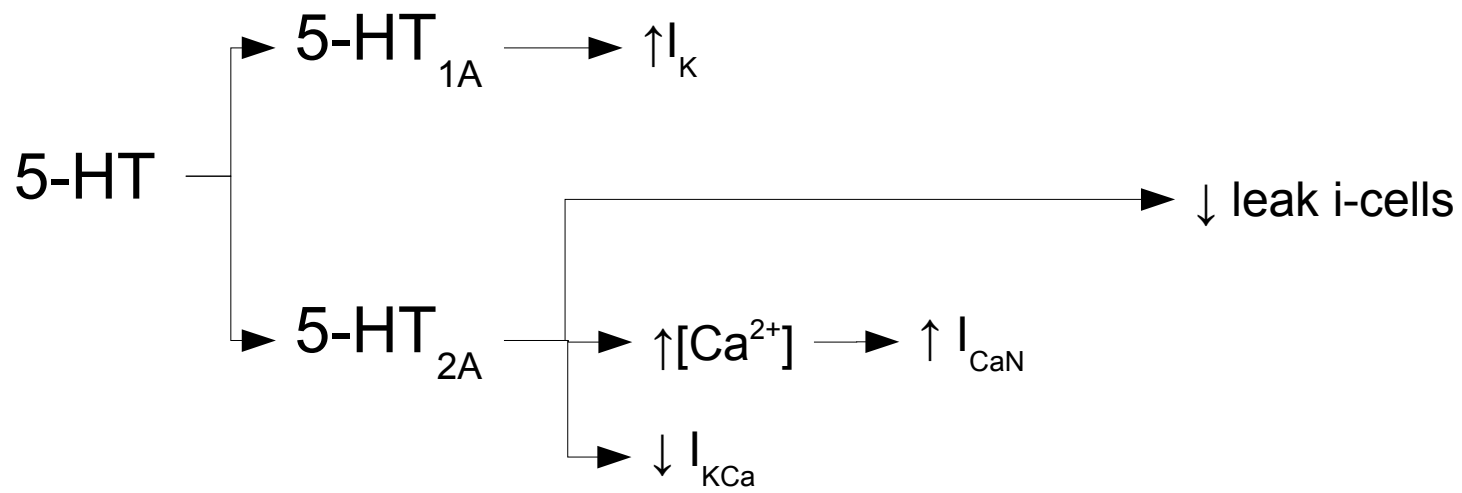
# Sensitivity to cellular mechanisms

- $I_{CaN}$  stabilizes persistent activity (Tegnér et al. 2002)
- $I_{KCa}$  destabilizes persistent activity
- Neural excitability stabilizes persistent activity but destabilizes spontaneous activity

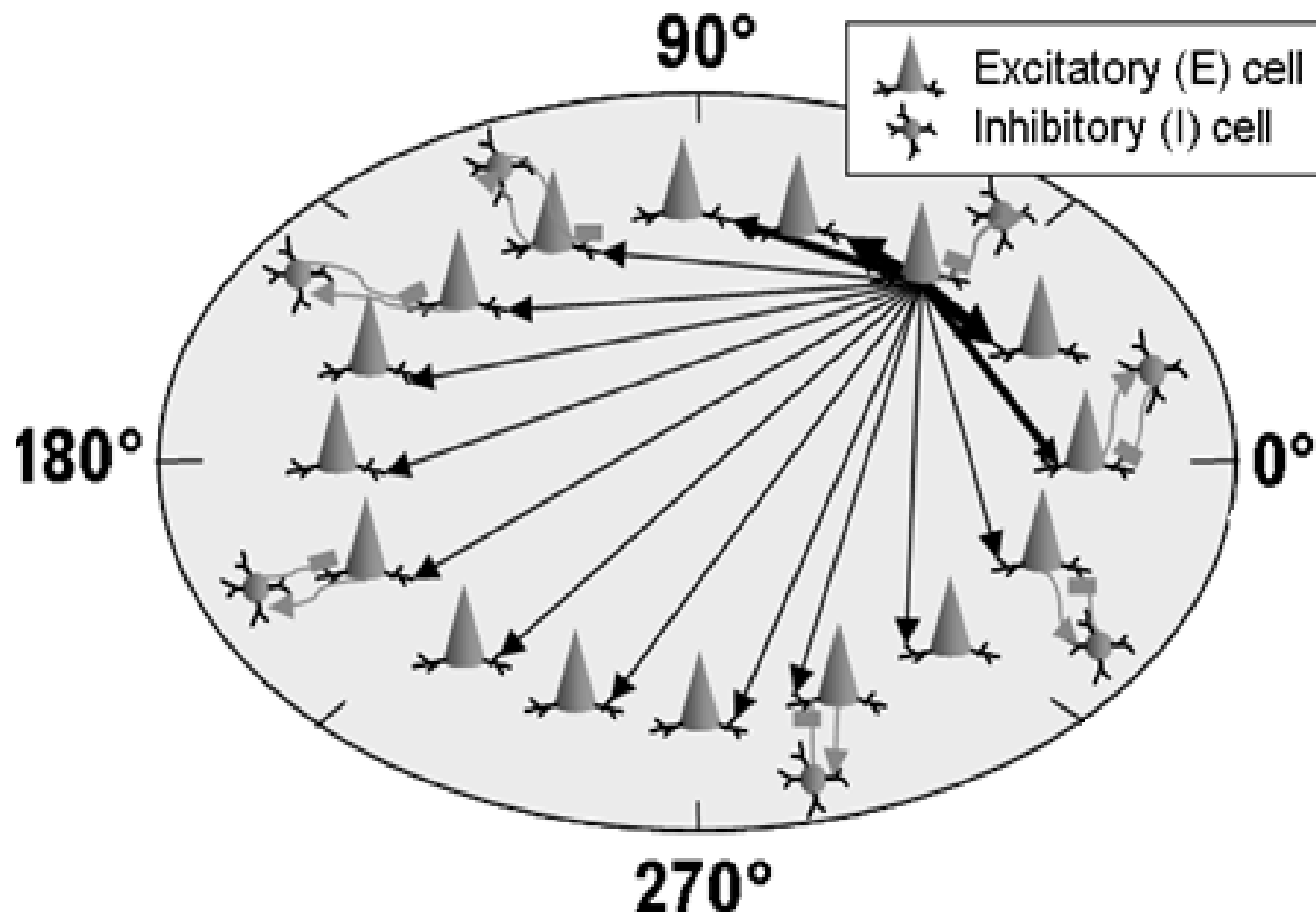


# Serotonin modulates cortical physiology *in vitro*

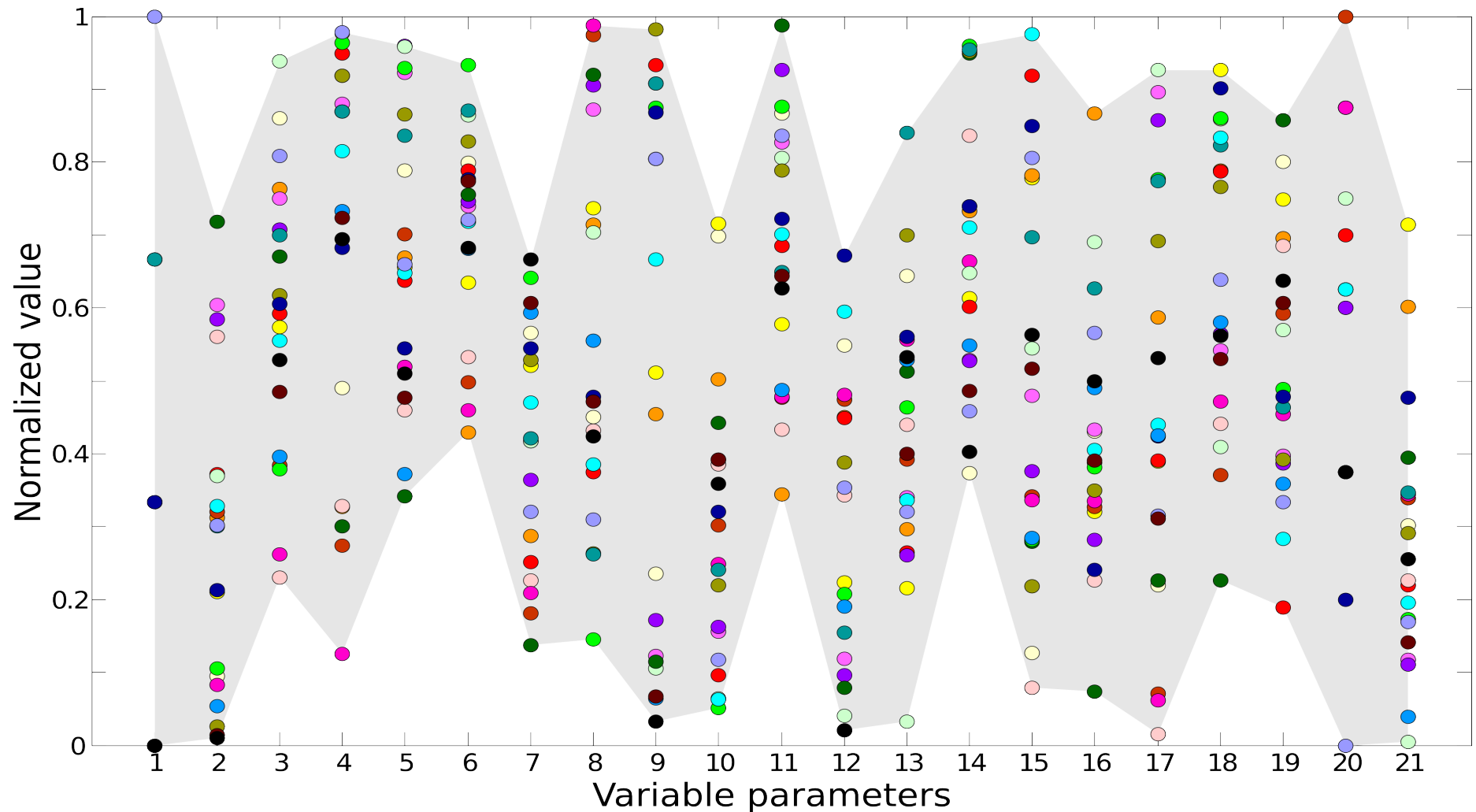




# 5-HT modulated networks



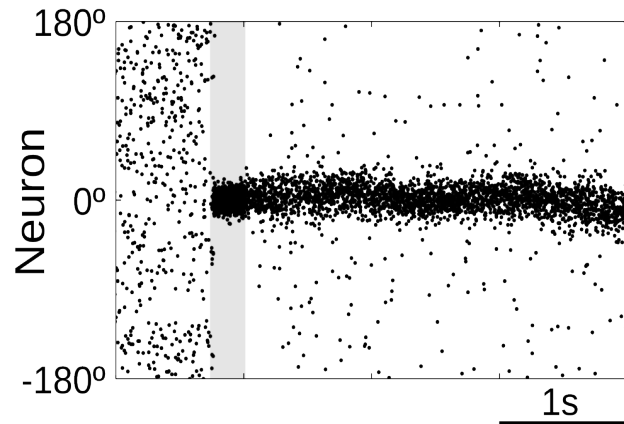
# 20 networks with diverse parameters but similar function



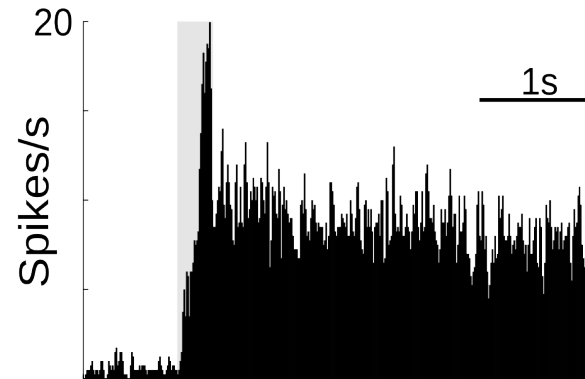


# Physiological effects of tonic and phasic 5-HT

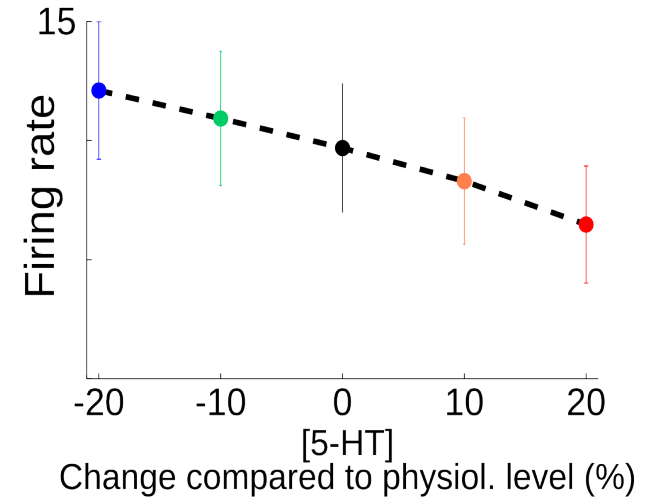
**A** Tonic 5-HT



**B**

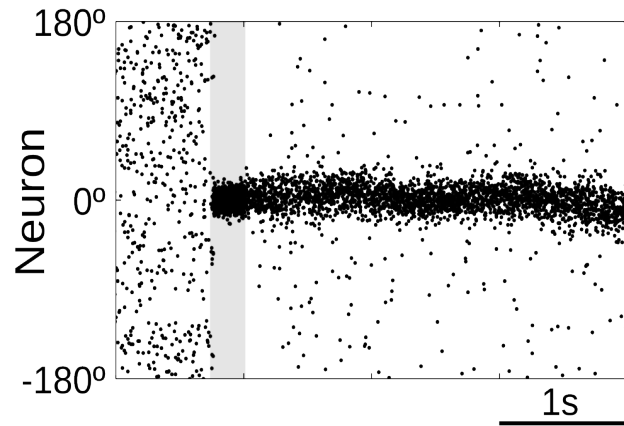


**C**

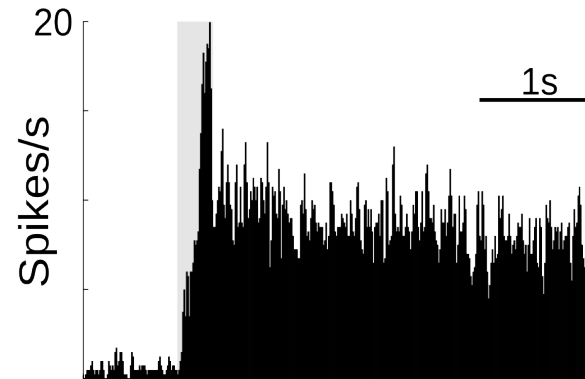


# Physiological effects of tonic and phasic 5-HT

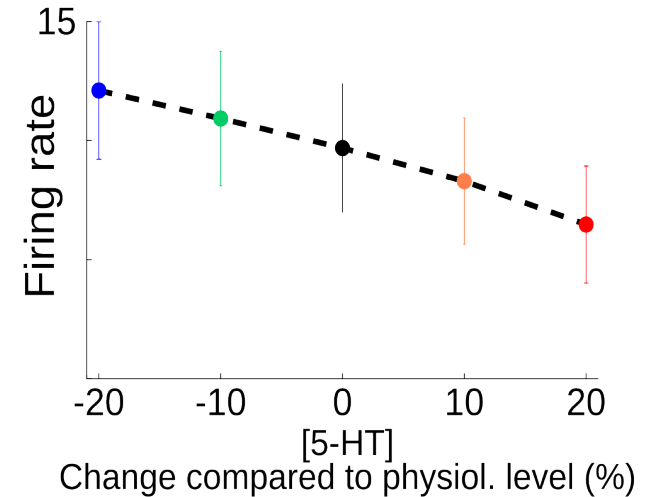
**A Tonic 5-HT**



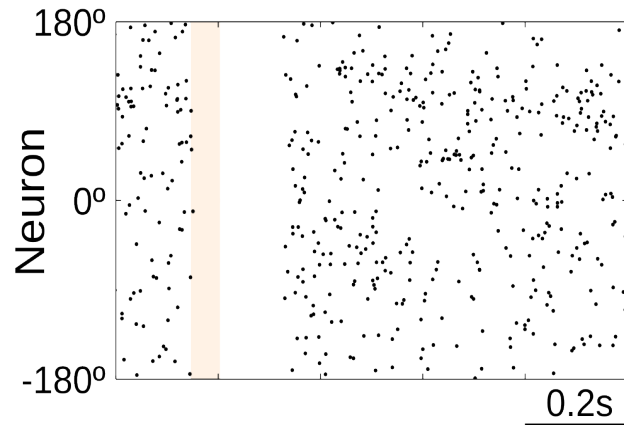
**B**



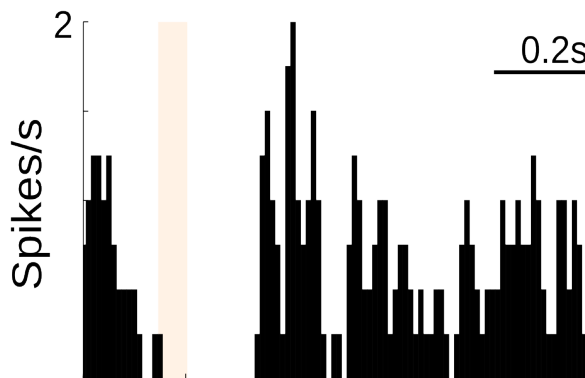
**C**



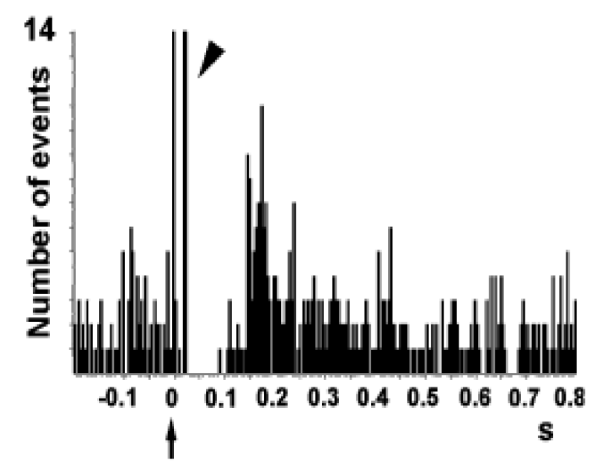
**D Phasic 5-HT**



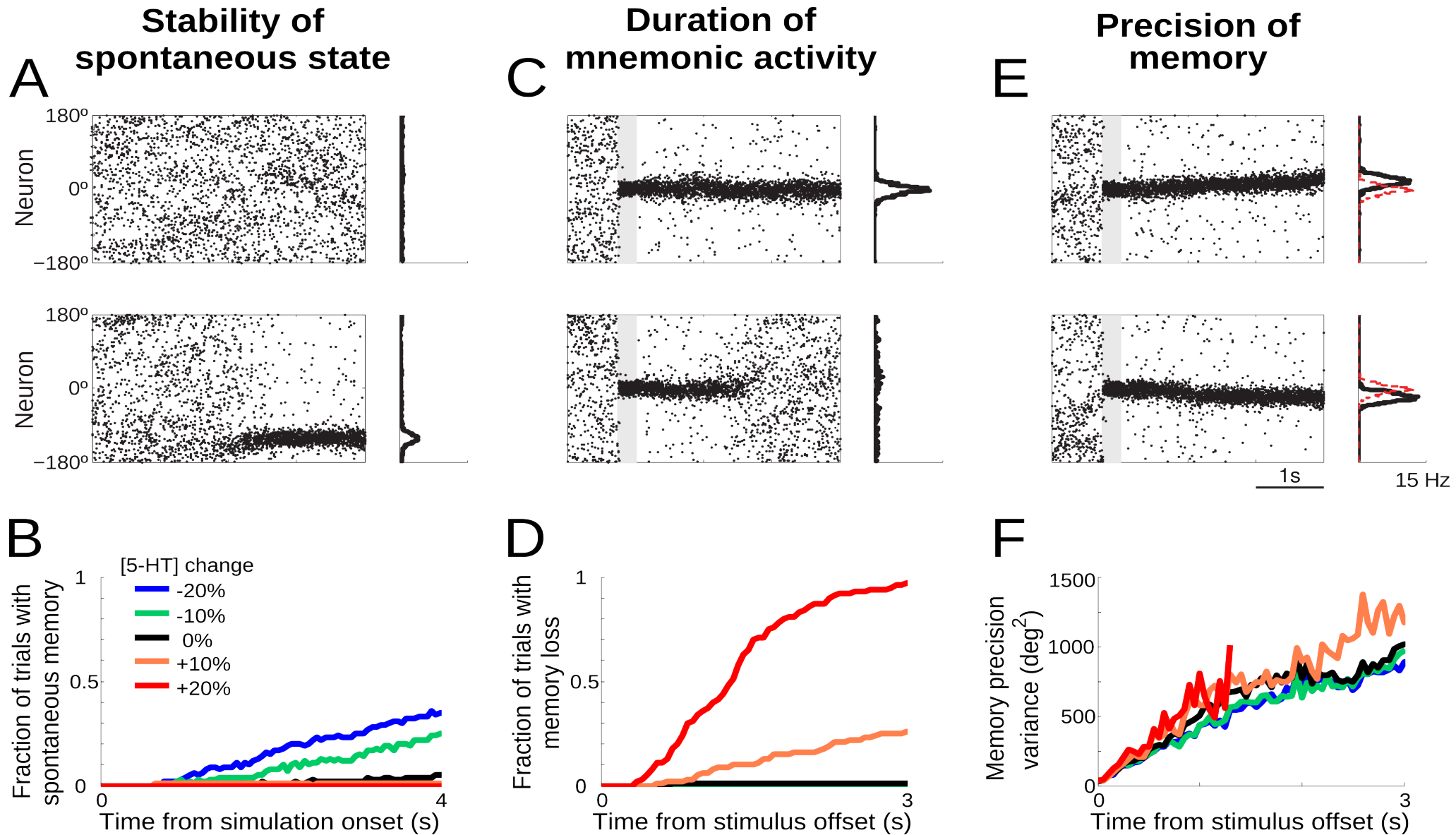
**E**



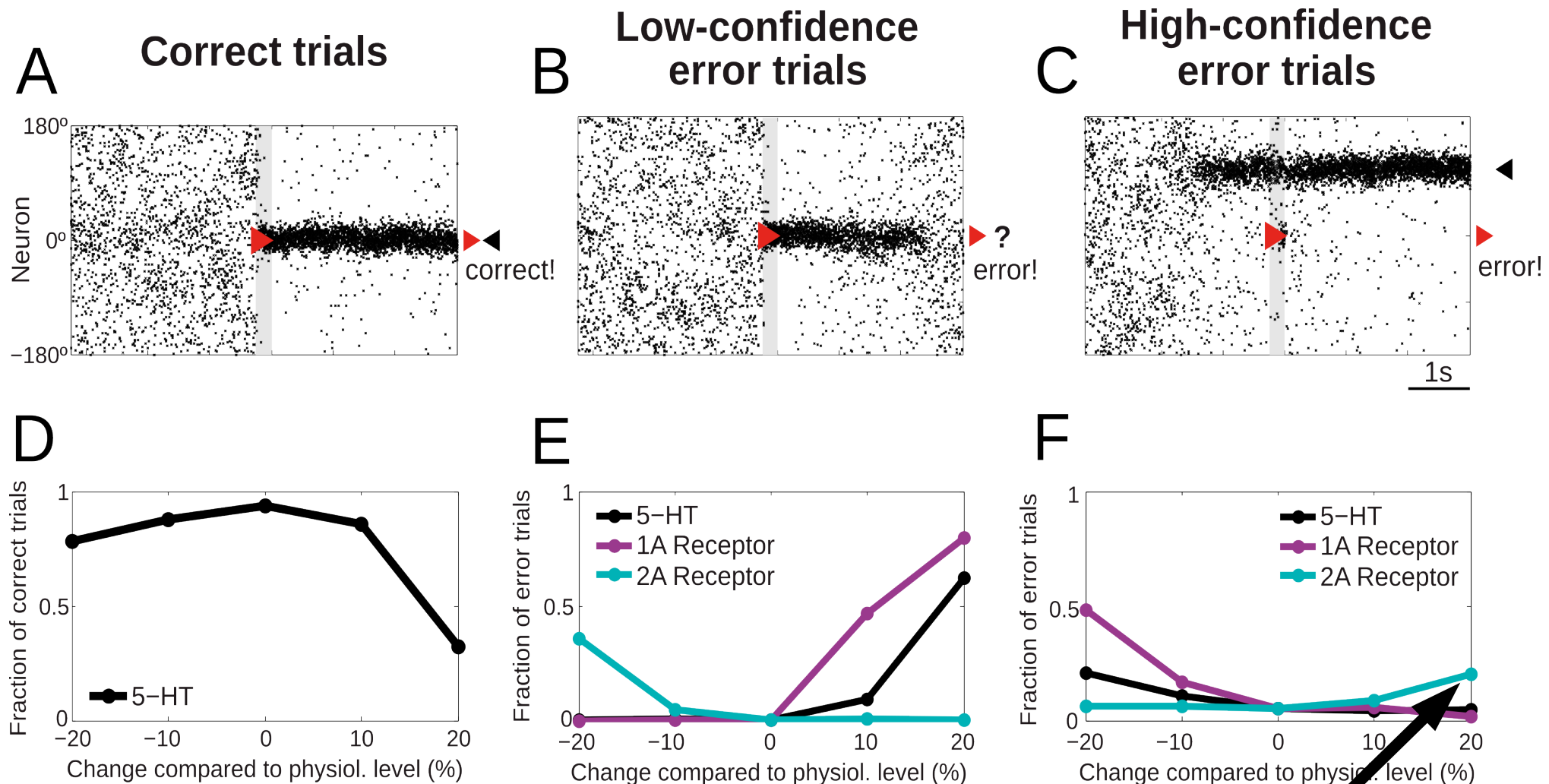
**F**



# Effects of 5-HT modulation on the stability of WM states

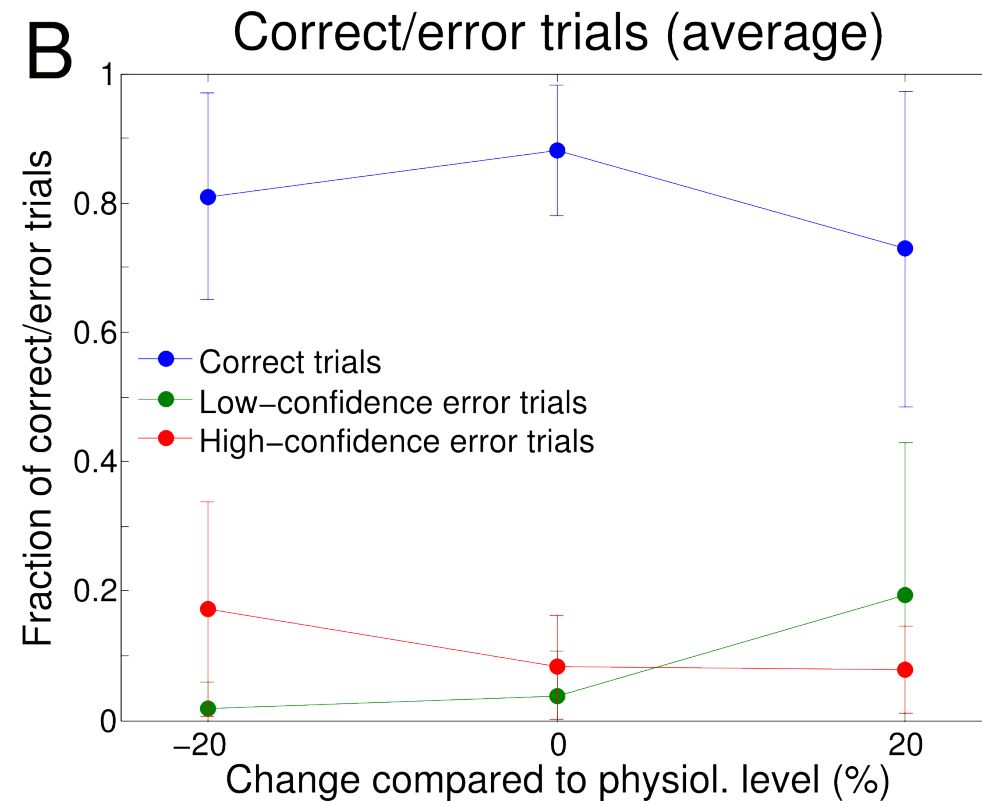
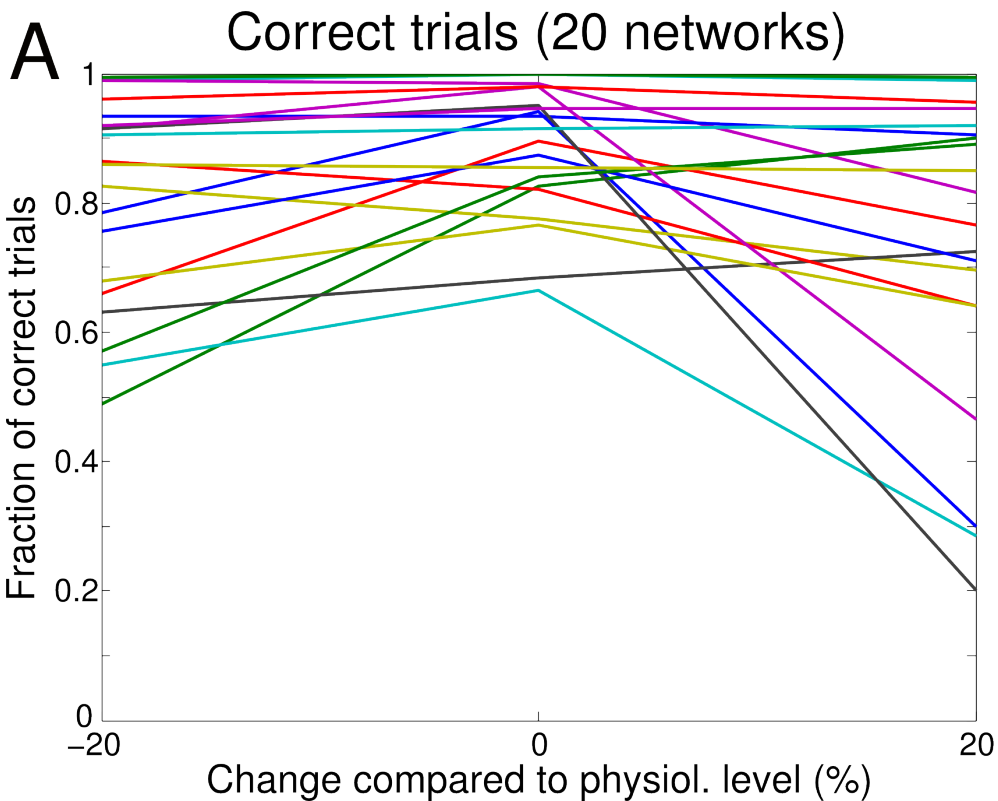


# Behavior: 5-HT affects WM in $\cap$ -shape via 5-HT<sub>1A</sub> receptors

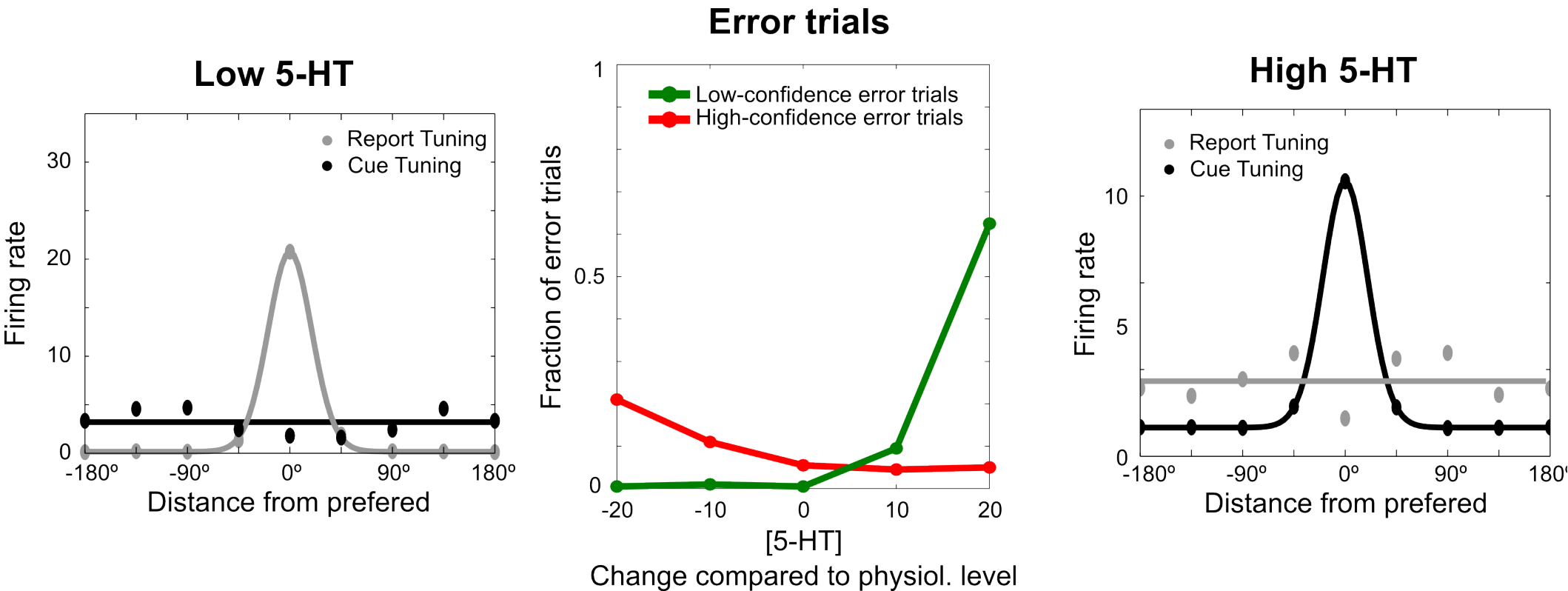


5-HT<sub>2A</sub> agonists induce “false memories”

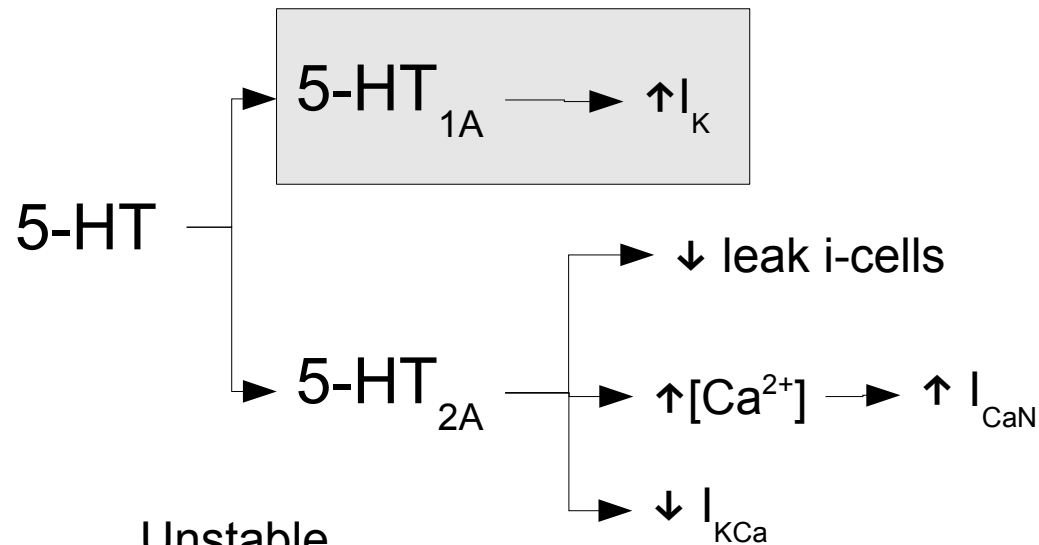
# Behavior: Confidence classification reveals 5-HT effects in WM



# Physiology: 5-HT modulates neural tuning to cue and response

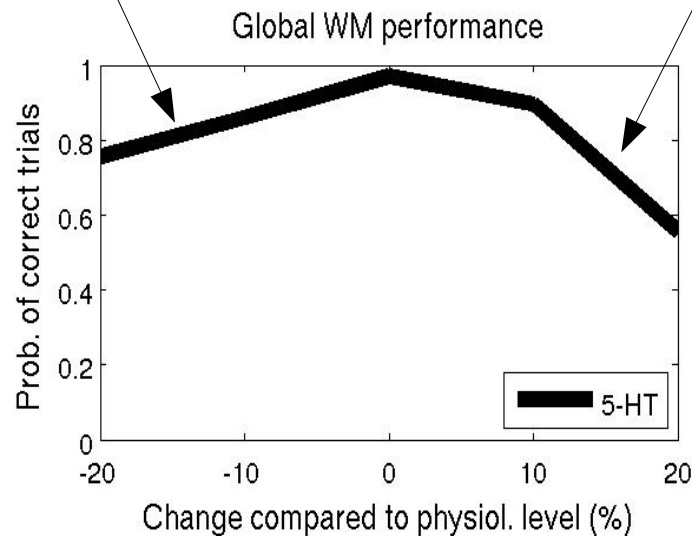


# Main action through $5\text{-HT}_{1A} \sim$ modulation of e-cell excitability

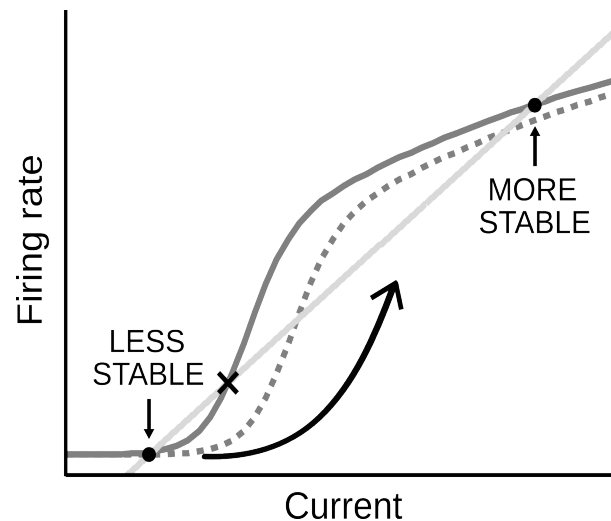


Spontaneous  
bumps

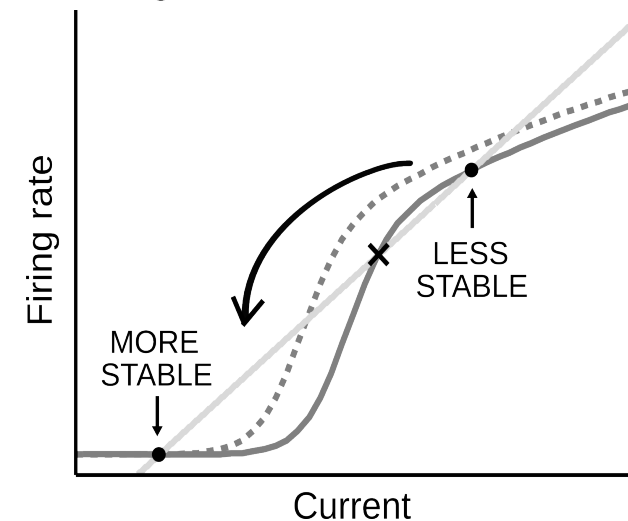
Unstable  
bumps



Low 5-HT → More excitable



High 5-HT → Less excitable

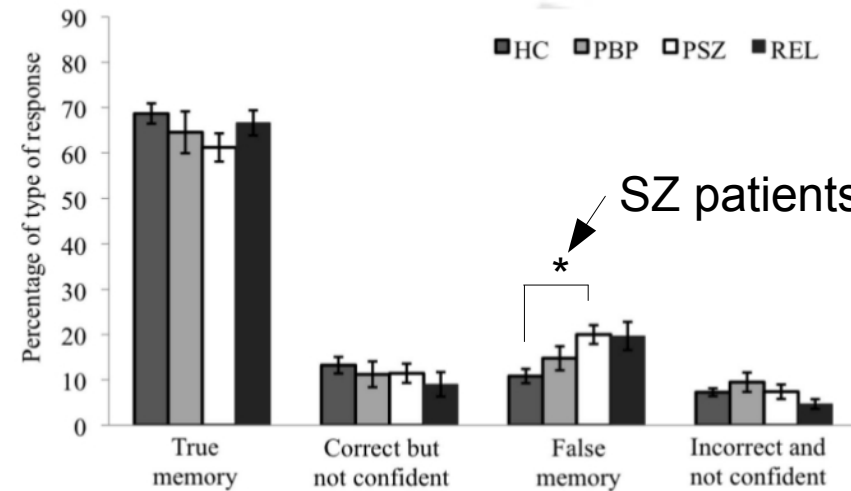


# Predictions I

- 5-HT impairs spatial WM in  $\cap$ -shape. This could underlie the conflicting psycho-pharmacological results of 5-HT and WM.
- 5-HT increases induce low-confidence errors
- 5-HT reductions induce high-confidence errors
- Same effect for 5-HT<sub>1A</sub> modulation but opposite effect for 5-HT<sub>2A</sub> modulation
- Stronger (weaker) neuronal delay selectivity to cue than response in error trials for high (low) 5-HT
- General mechanism, it will apply to any neuromodulator of cellular excitability



# Schizophrenia and WM errors (Sohee Park)

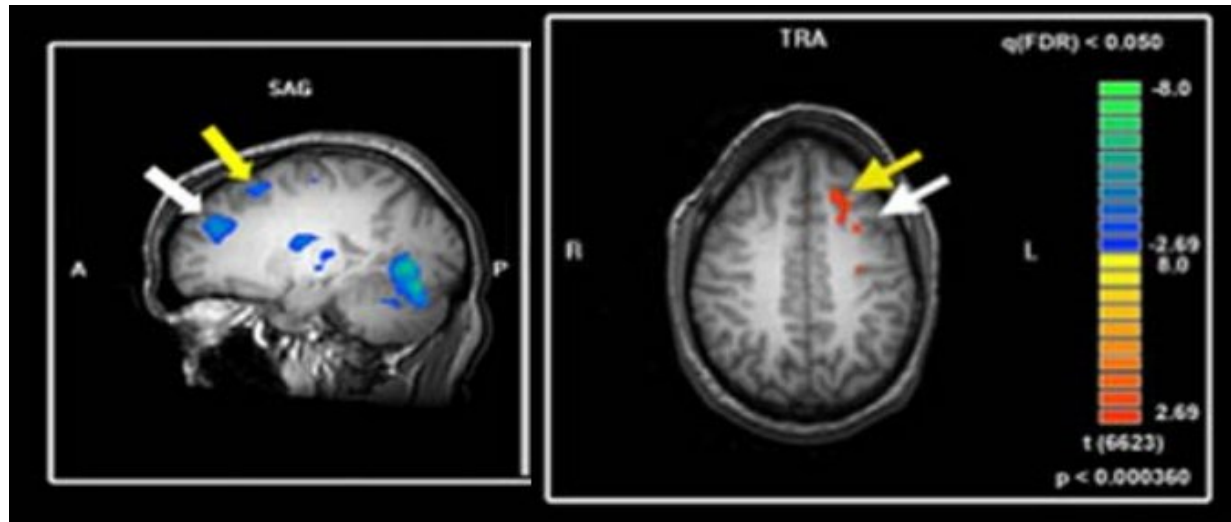


SZ patients make more high-confidence errors, “false memories”

Mayer and Park, J Abn Psychol 2012

Correct trials

False memory trials



Lee and Park, PLoS ONE 2008

# “Psychotic” attractor networks

- (...) Speech is disorganized both in people suffering from mania and from schizophrenia (...) The distinction between the two disturbances is likened, respectively, to that between,
  - Noisy network behavior, whereby noise provokes 'unregulated' shifts from one attractor to another, and
  - Spurious states, which are 'stable' patches of attractor fragments

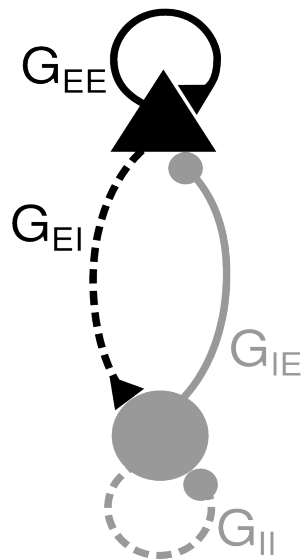
Amit D.J. “Modeling Brain Function” Cambridge Univ Press 1989  
Hoffman R.E. Arch. Gen. Psychiatry 44:178, 1987

Loh M., Rolls E.T., Deco G. PloS Comput Biol 2007

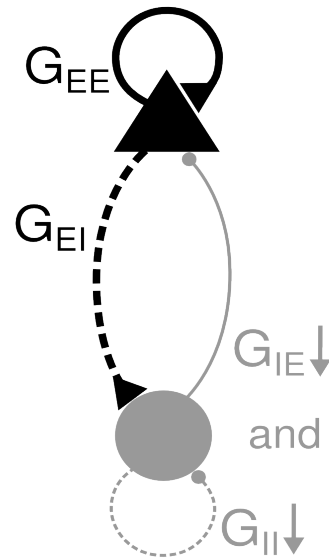
# “Psychotic” WM networks

- “disordered thought” symptoms → high incidence of spurious bumps, “false memories” (Lee et al. 2008)
- GABAergic hypothesis (Lewis et al. 2005)
- Glu hypothesis (Coyle 2006): hypofunctional NMDA

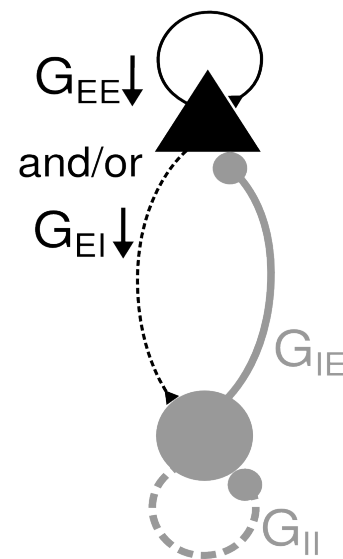
A Healthy



B SZ  
GABA hyp.

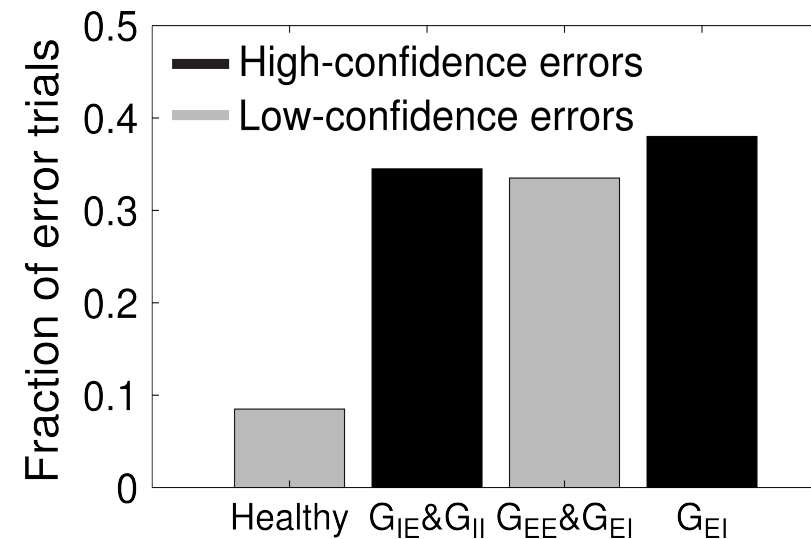
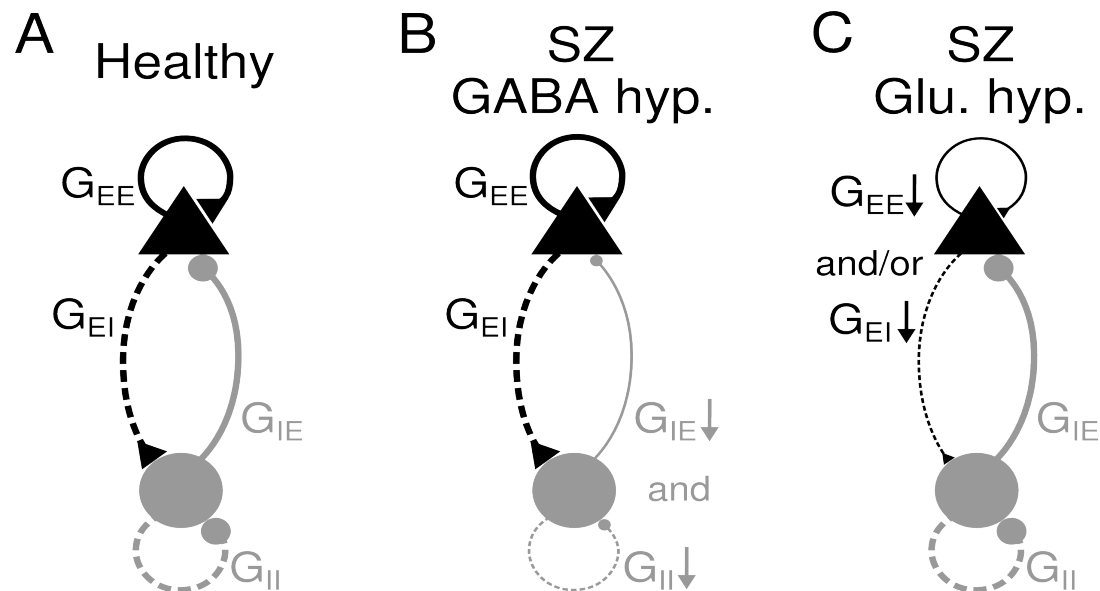


C SZ  
Glu. hyp.

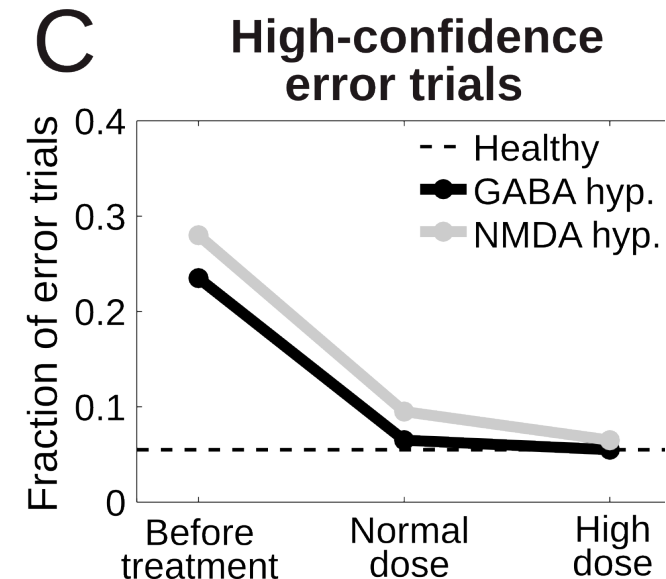
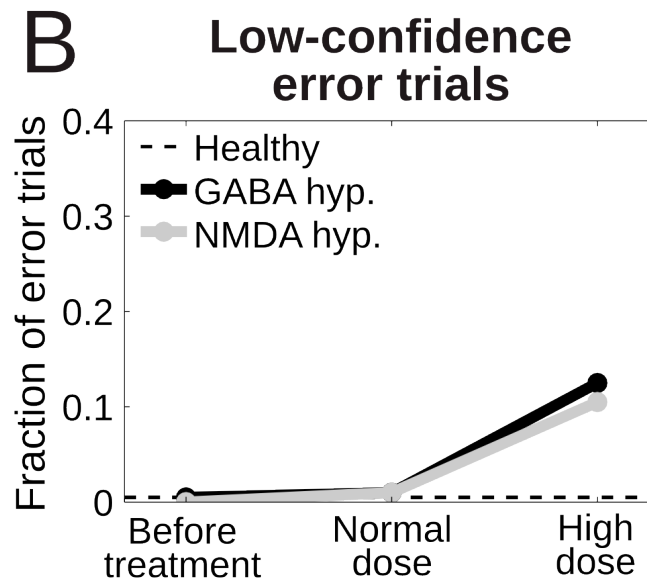
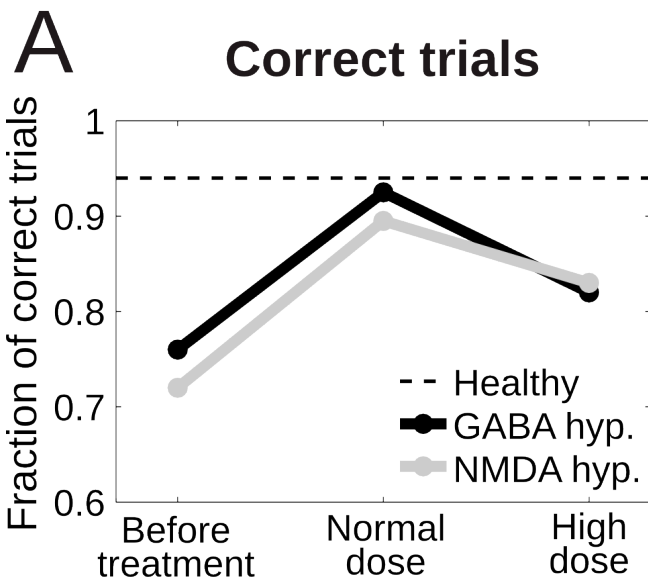


# “Psychotic” networks

- “disordered thought” symptoms → high incidence of spurious bumps, “false memories” (Lee et al. 2008)
- GABAergic hypothesis (Lewis et al. 2005): 60%  $g_{GABA}$
- Glu hypothesis: hypofunctional NMDA (95%  $g_{E \rightarrow E}$ , 88%  $g_{E \rightarrow I}$ )

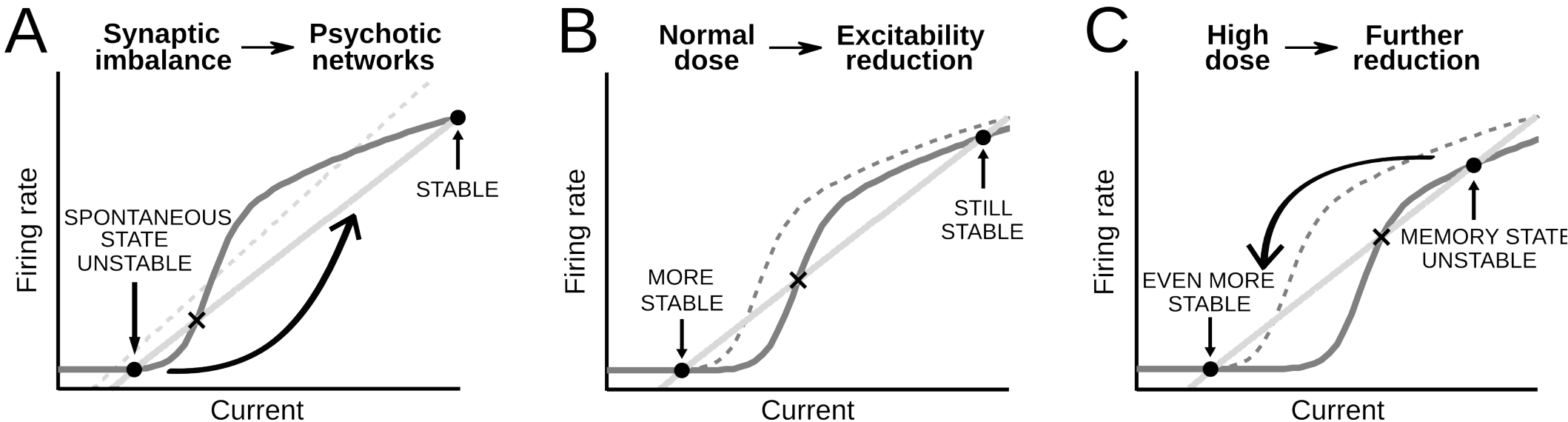


# Treating “psychotic” networks with atypical antipsychotic drugs



**Atypical antipsychotic treatment:** 5-HT<sub>1A</sub> agonist (5% increase) and 5-HT<sub>2A</sub> antagonist (10% reduction). High dose: changes doubled.

# A general mechanism for WM tuning in SZ



Many receptors, many drugs converge onto one mechanism: excitability modulation

# Predictions II

- Antipsychotic treatment targeting 5-HT receptors reduces “false memories”, but...
- High-dose antipsychotics impair WM via memory loss and distraction
- $\cap$ -shaped efficacy of 5-HT treatment may underlie inconclusive findings on neurocognitive advantages of 5-HT targeting antipsychotics
- Predictions general for any pharmacological treatment that reduces excitability of PFC neurons

Thanks to...

Maria Cano-Colino (IDIBAPS)

Rita Almeida (Karolinska)

Francesc Artigas (IIBB – IDIBAPS)





