

Synaptic basis of reduced serial dependence in anti-NMDAR encephalitis and schizophrenia

BioRTC/Simons Computational Neuroscience
Course

Albert Compte
IDIBAPS, Barcelona

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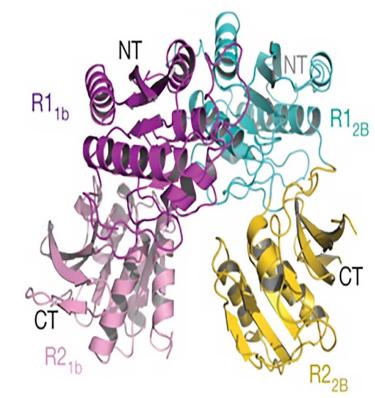
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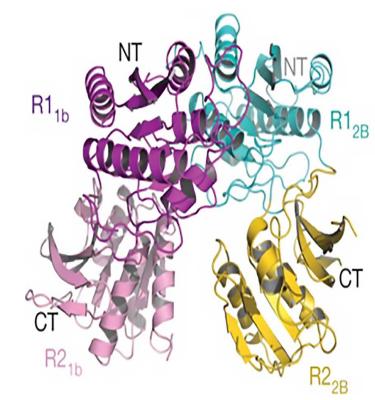
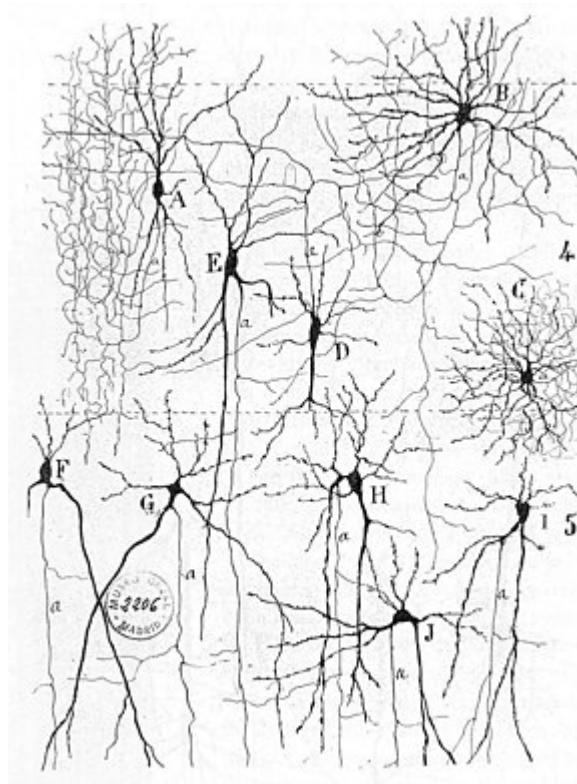


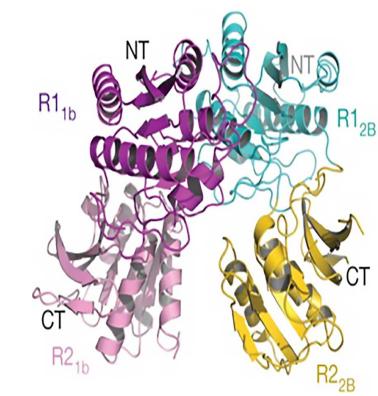
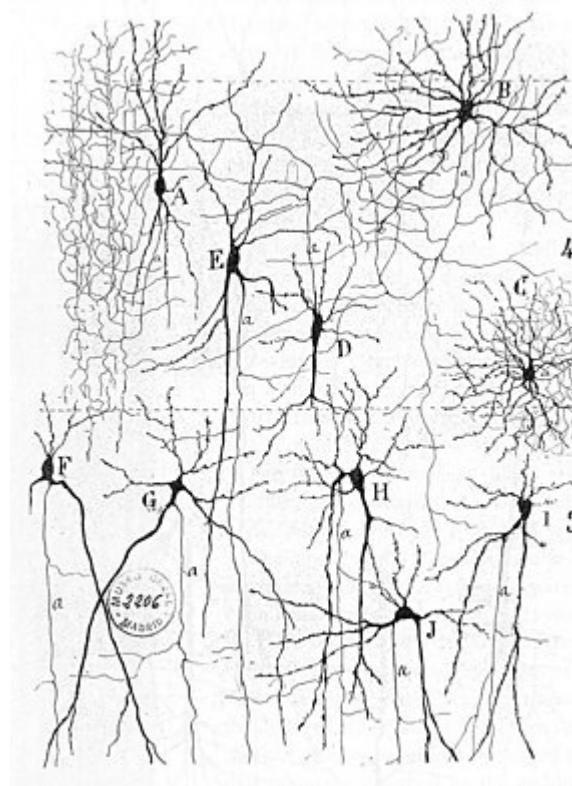
Heike Stein



Joao Barbosa



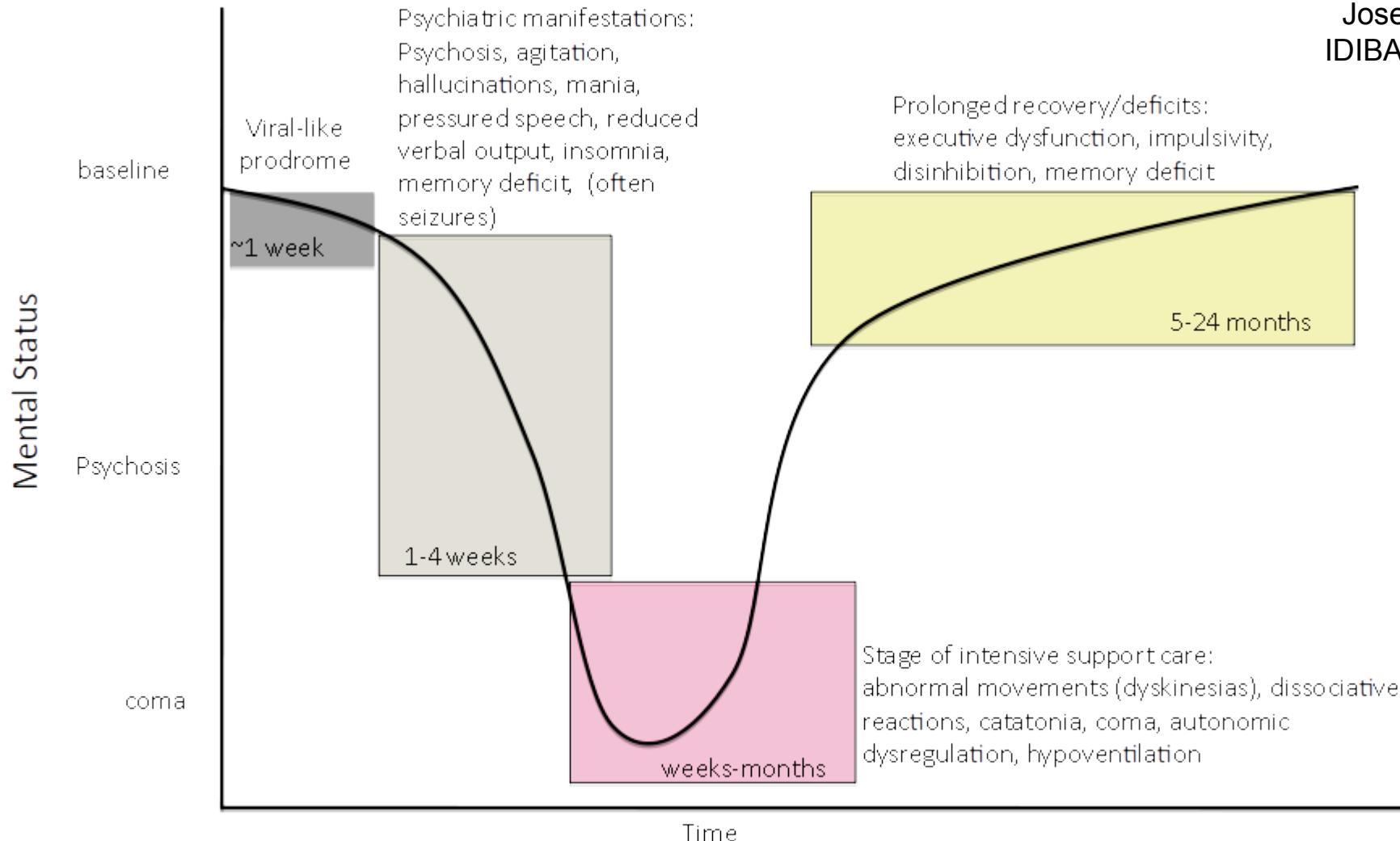




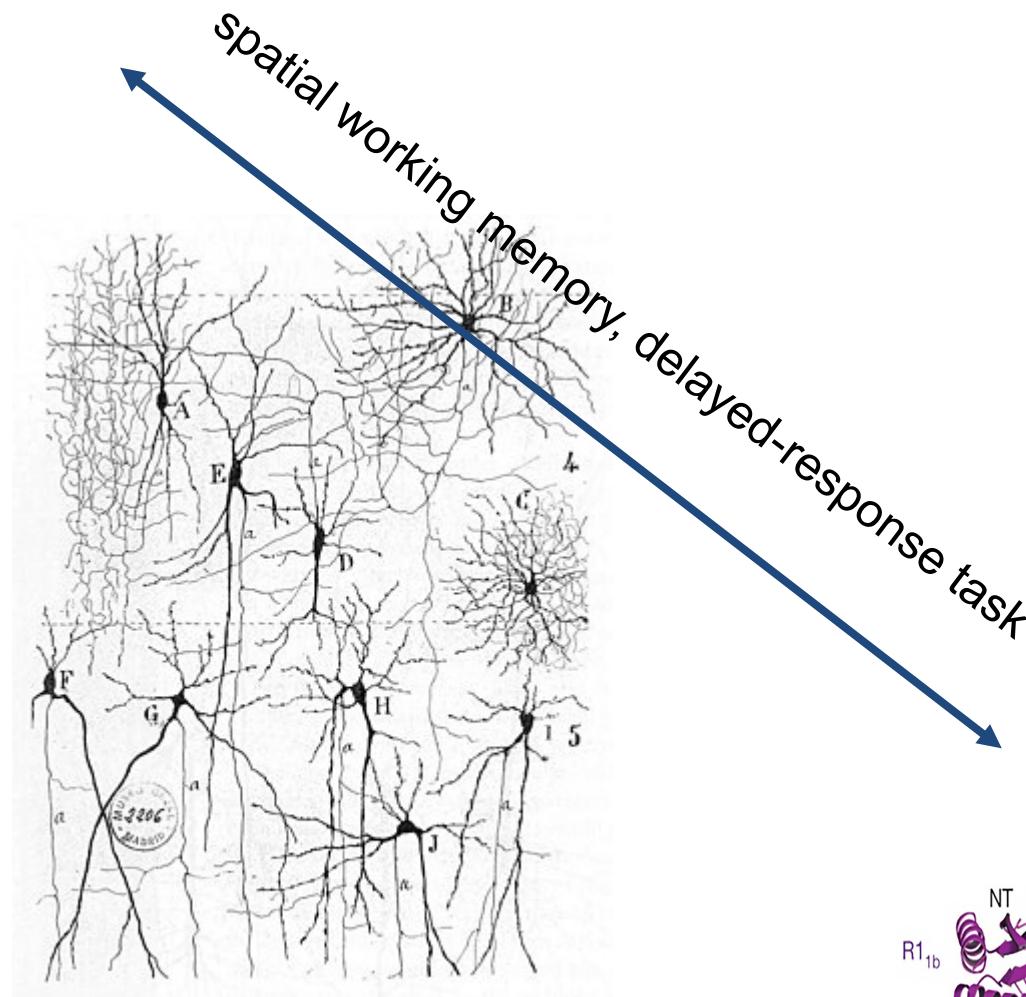
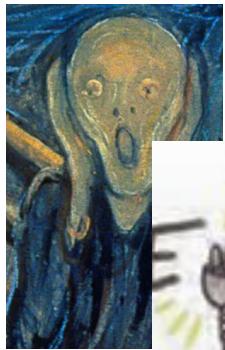
Symptoms and course of anti-NMDAR encephalitis



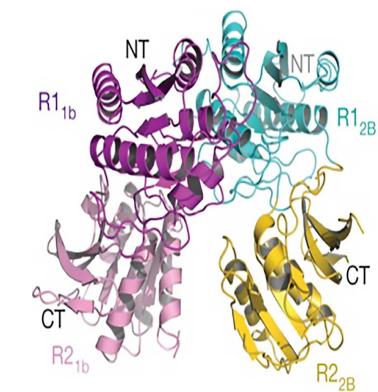
Josep Dalmau
IDIBAPS, UPenn



Kayser & Dalmau. Curr Psychiatry Rev 2011;7:189-193



spatial working memory, delayed-response task



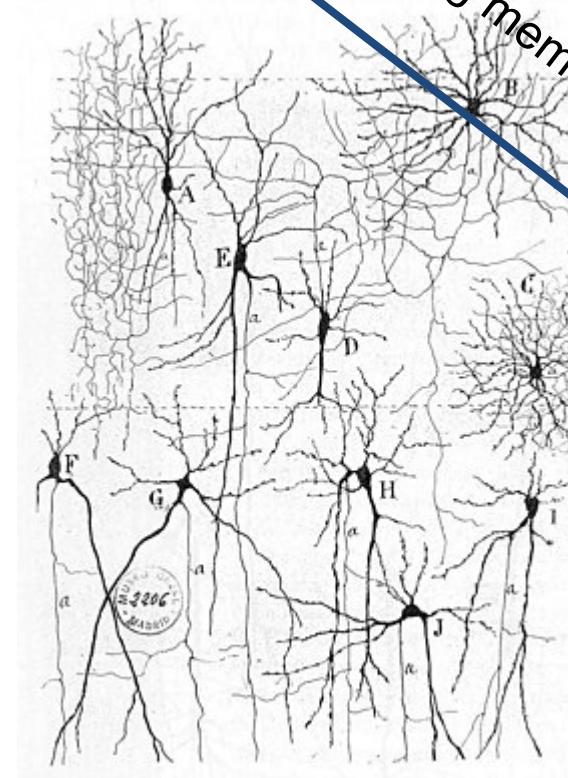


catch: too easy?

EEG decoding



Joan Santamaría
IDIBAPS



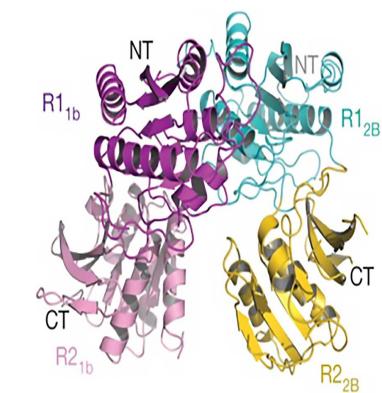
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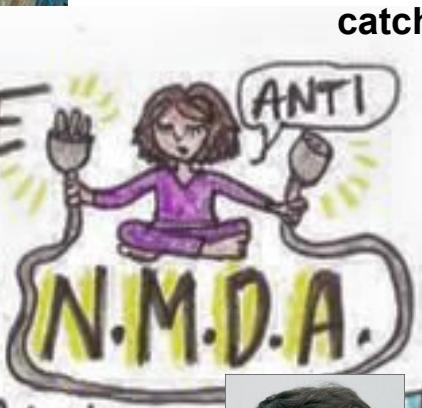
biophysical
network models

monkey
electrophysiology

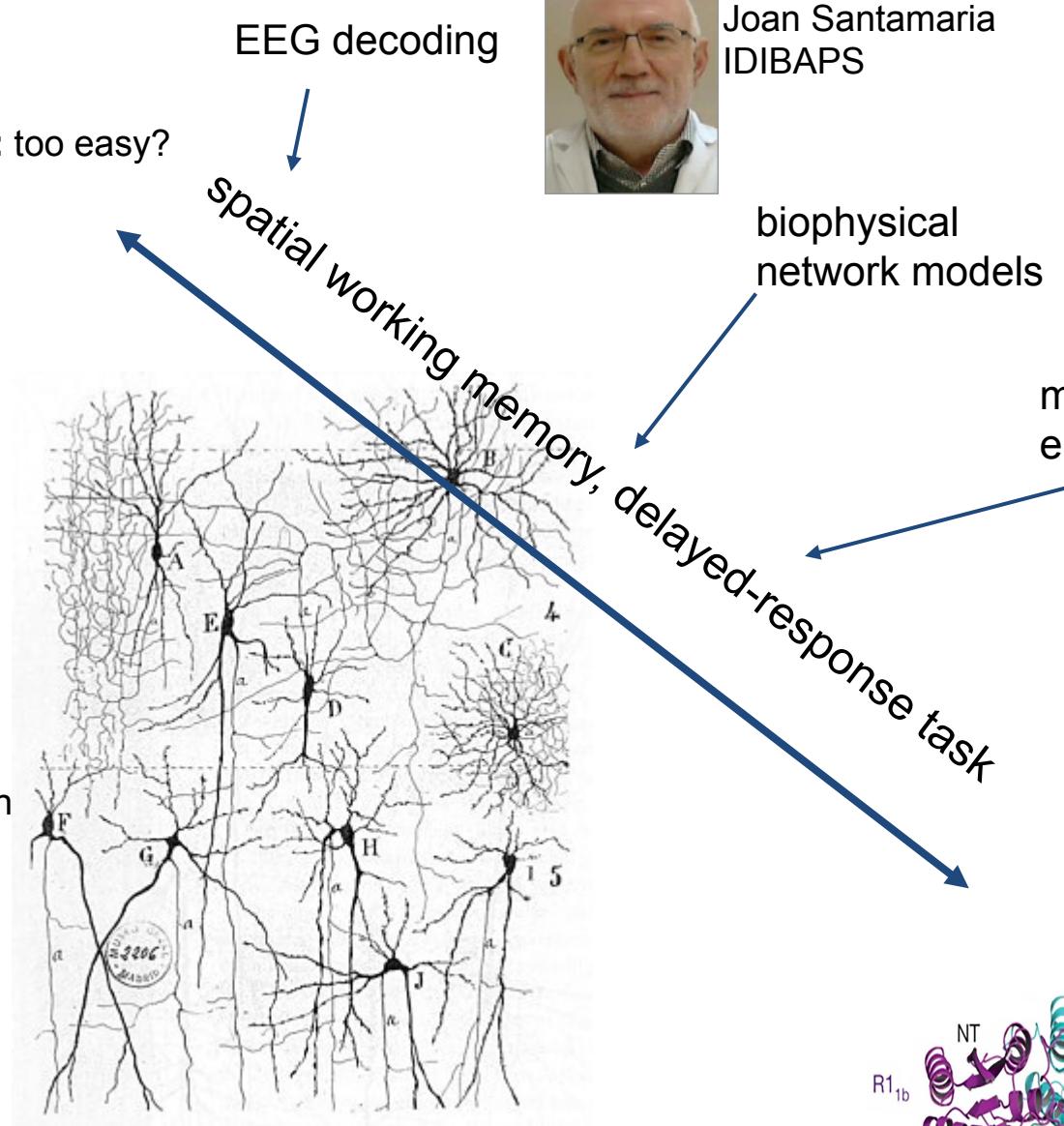


C. Constantinidis
Vanderbilt Univ.





catch: too easy?



Joan Santamaria
IDIBAPS



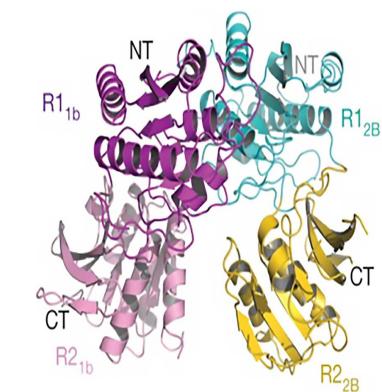
Josefina Castro
IDIBAPS



Josep Dalmau
IDIBAPS, UPenn



C. Constantinidis
Vanderbilt Univ.

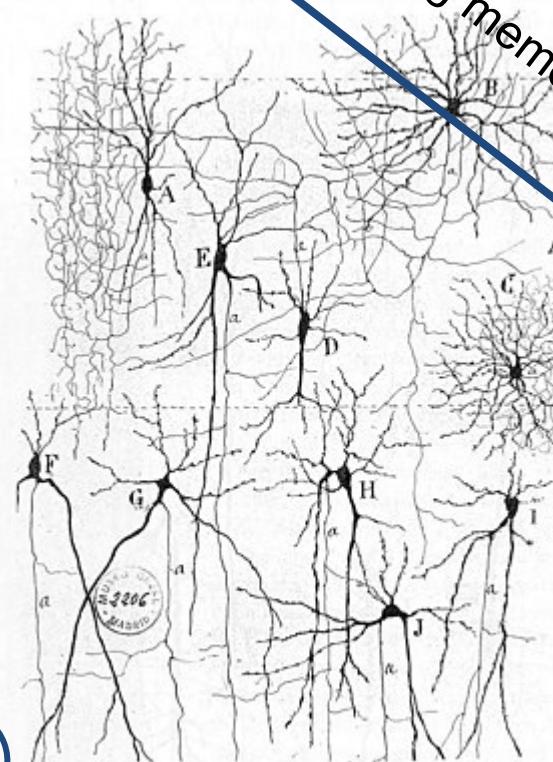




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IDIBAPS



EEG decoding

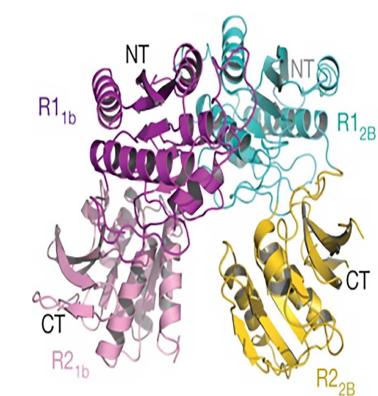
spatial working memory, delayed-response task

biophysical network models

monkey electrophysiology



C. Constantinidis
Vanderbilt Univ.



rodents: NMDAR - circuit - behavior - symptoms



Josefina Castro
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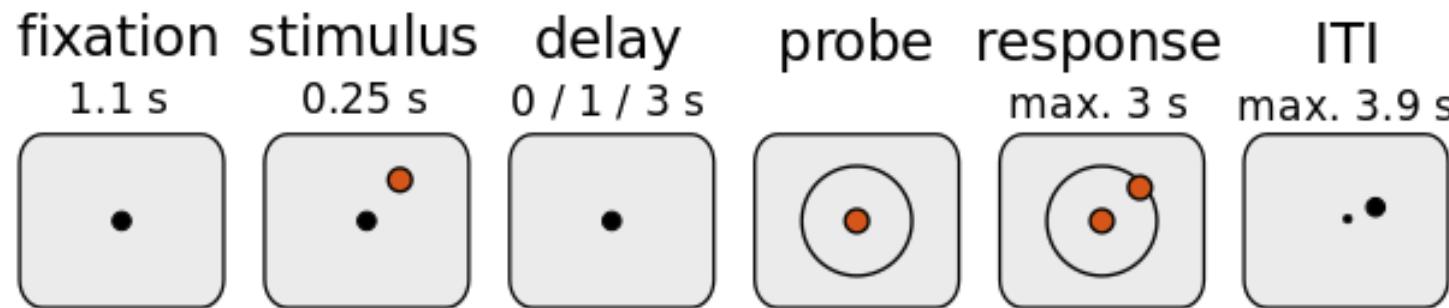


Josep Dalmau
IDIBAPS, UPenn



Jaime de la Rocha
IDIBAPS

Spatial working memory task



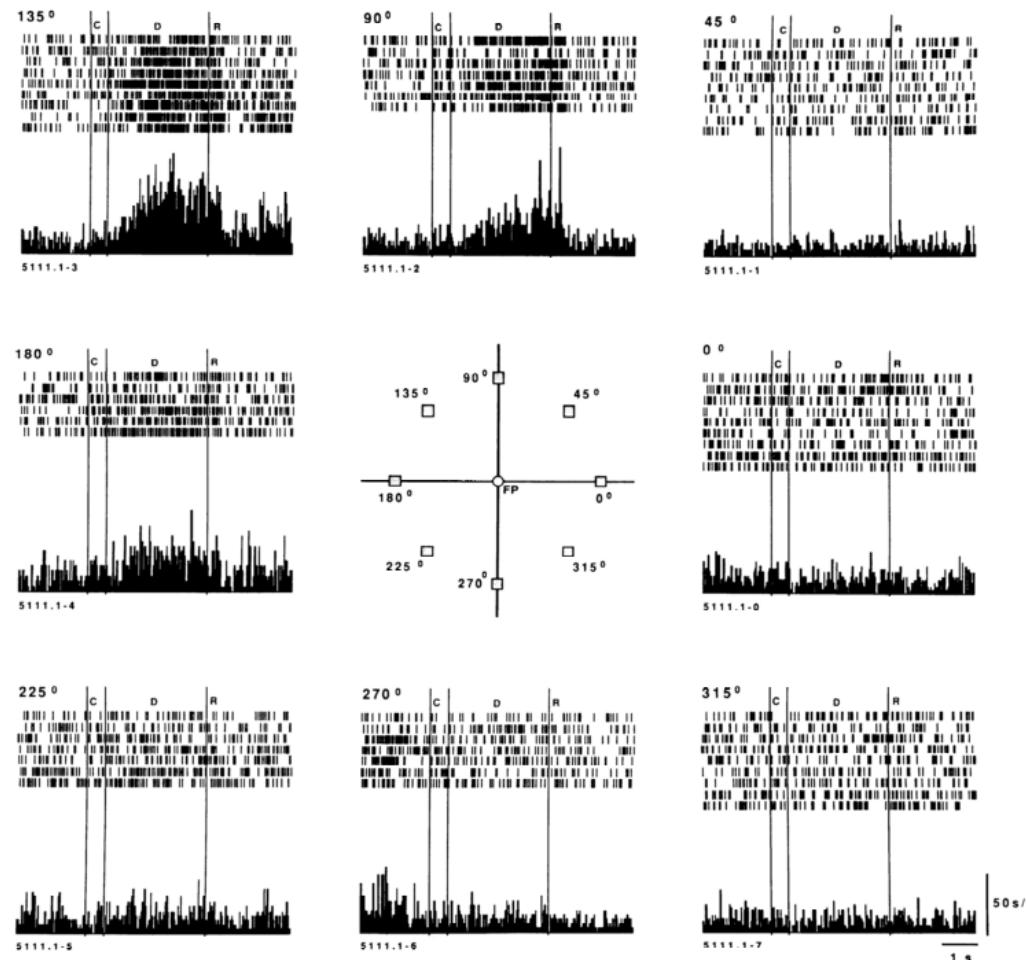
Cohort

healthy controls (ctrl, EEG n = 22)

anti-NMDAR encephalitis (enc, EEG n = 27)

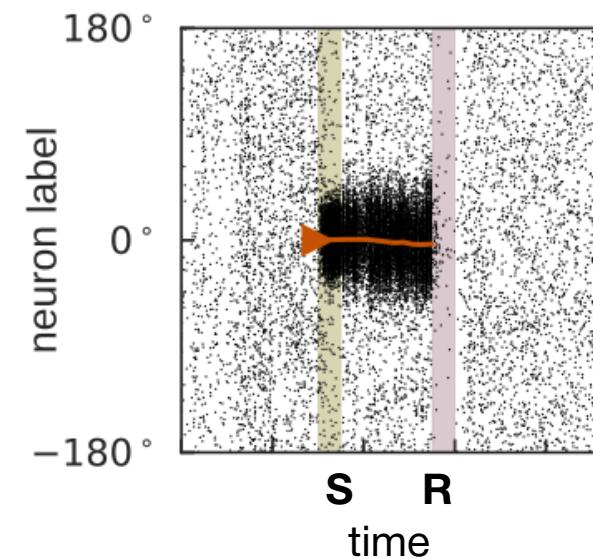
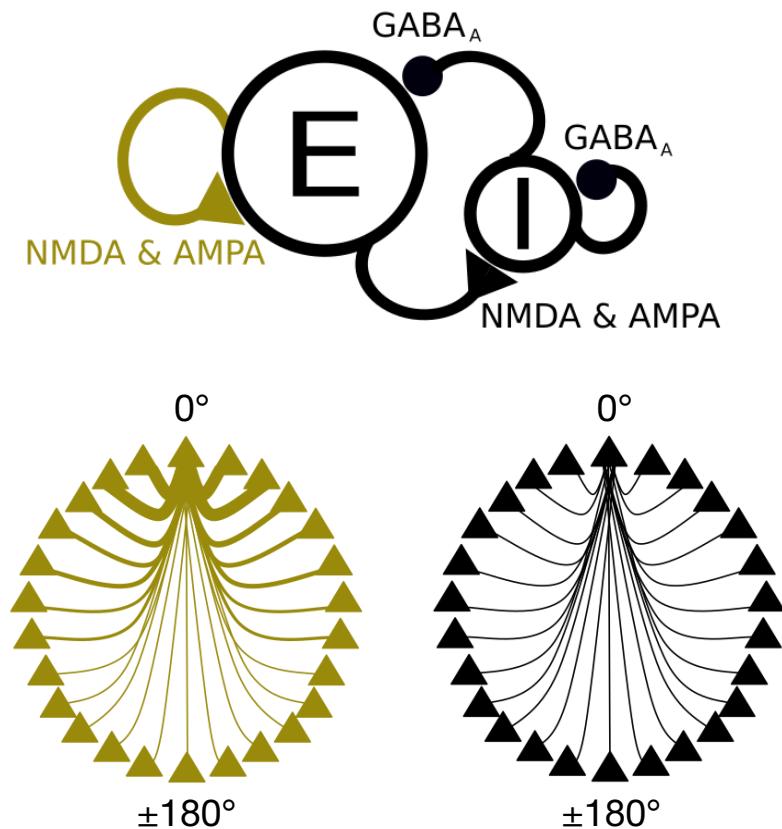
schizophrenia (schz, EEG n = 19)

Monkey electrophysiology



Sustained delay activity
(Funahashi et al., *J Neurophysiol*, 1989)

Computational network model

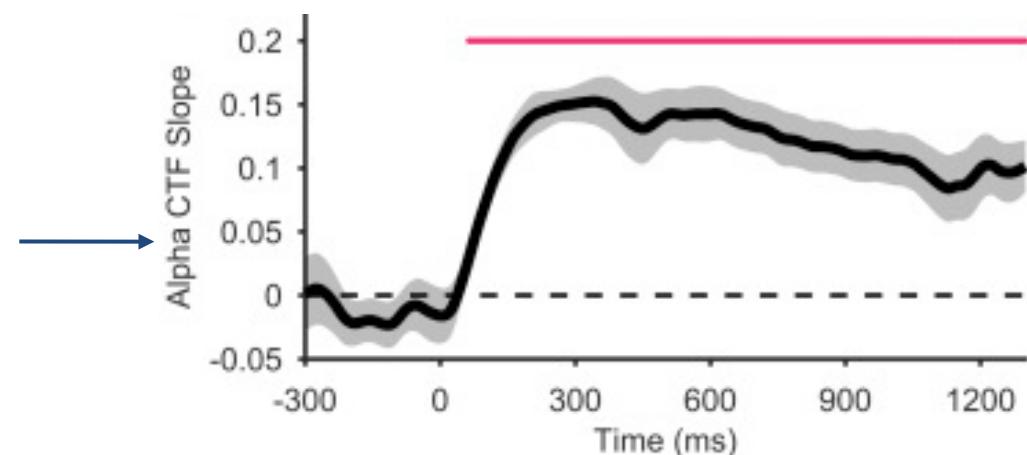


Compte et al. Cereb Cortex 2000

Electrophysiological readout of the task



decode stimulus
location from the
spatial distribution of
EEG-power in alpha
band



Foster et al. J Neurophysiol 2016
Foster et al. Curr Biol 2017

Objectives, questions, hypotheses

- Identify quantifiable behavioral deficits in spatial working memory in patients recovering from anti-NMDAR encephalitis and patients with stabilized schizophrenia
 - Are there still analogies between anti-NMDAR encephalitis and schizophrenia following stabilization after acute periods?

(Stein*, Barbosa* et al. *Nat Commun* 2020)

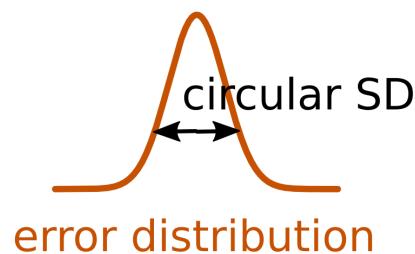
- formulate plausible neural circuit alterations that give rise to the behavioral deficits, and their link to NMDARs
 - What is the main neural circuit alteration related to spatial working memory in the stabilized phase of the diseases?

(Stein*, Barbosa* et al. *Nat Commun* 2020, unpublished)

Main hypothesis: NMDAR are important for maintaining stable memories in computational models, so patients will have shorter memory span and weaker EEG signals in memory periods than controls

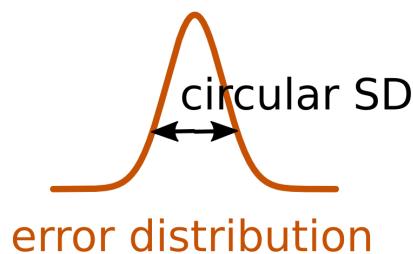
Quantifying working memory maintenance

response accuracy:

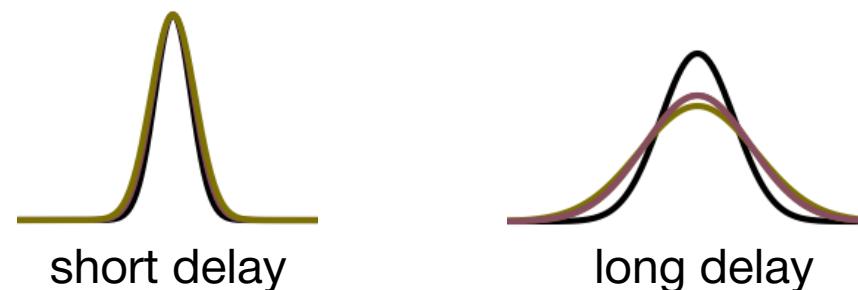


Quantifying working memory maintenance

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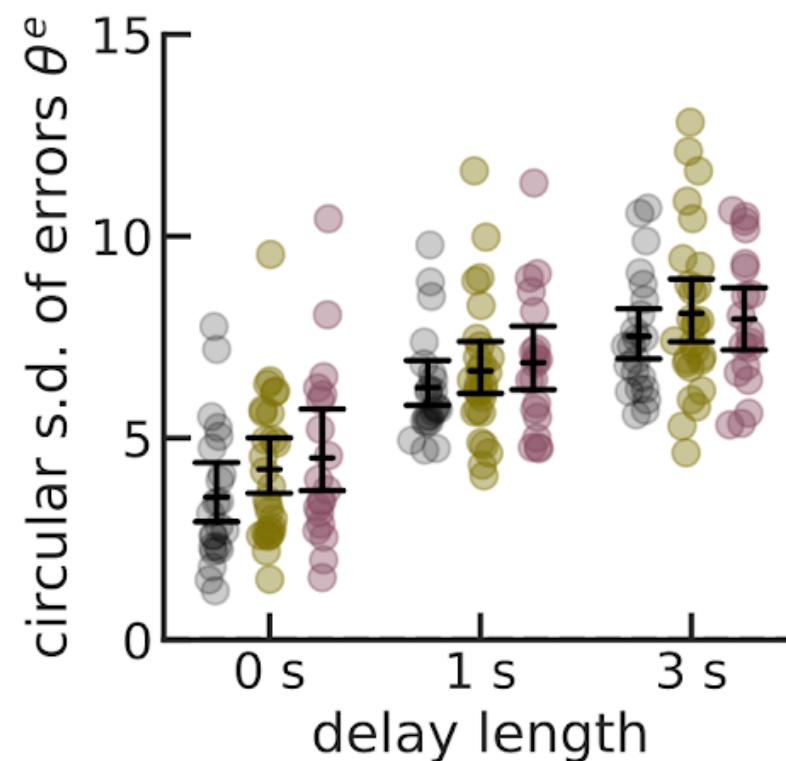
expected results:



as observed for schizophrenia in:

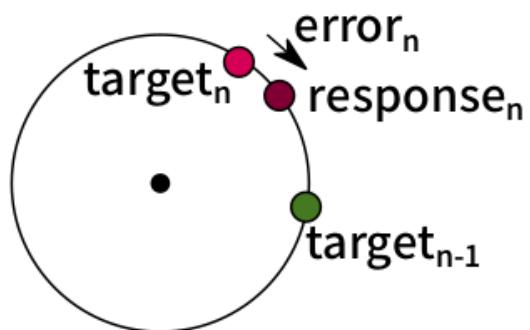
Starc et al., *Schiz Research*, 2016

Working memory accuracy is not affected by NMDAR dysfunction (for delays < 3s)



Quantifying inter-trial interference

serial dependence:

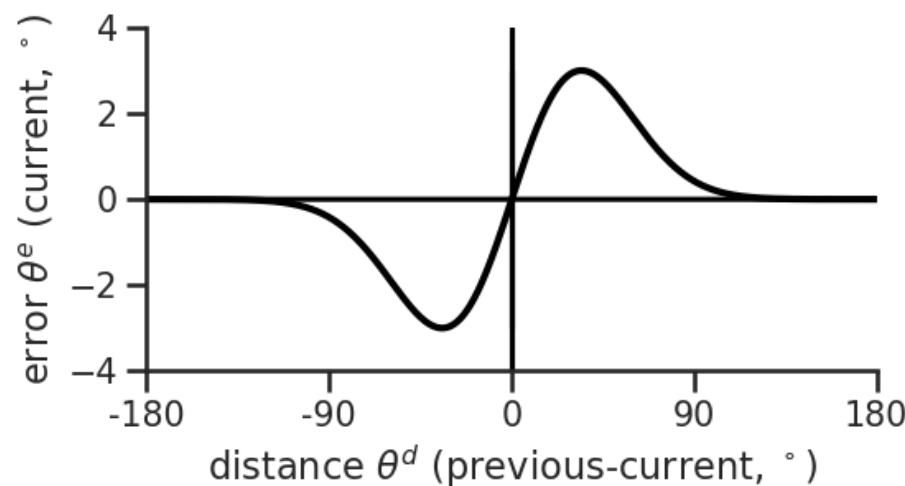
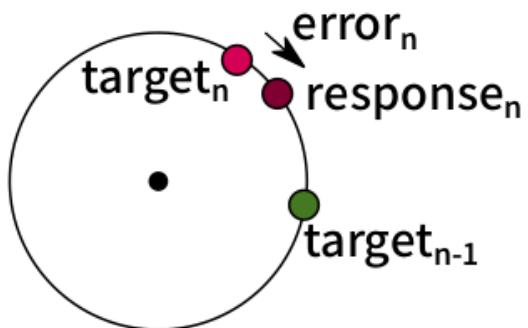


first described by

Fischer & Whitney, *Nat Neurosci*, 2014

Quantifying inter-trial interference

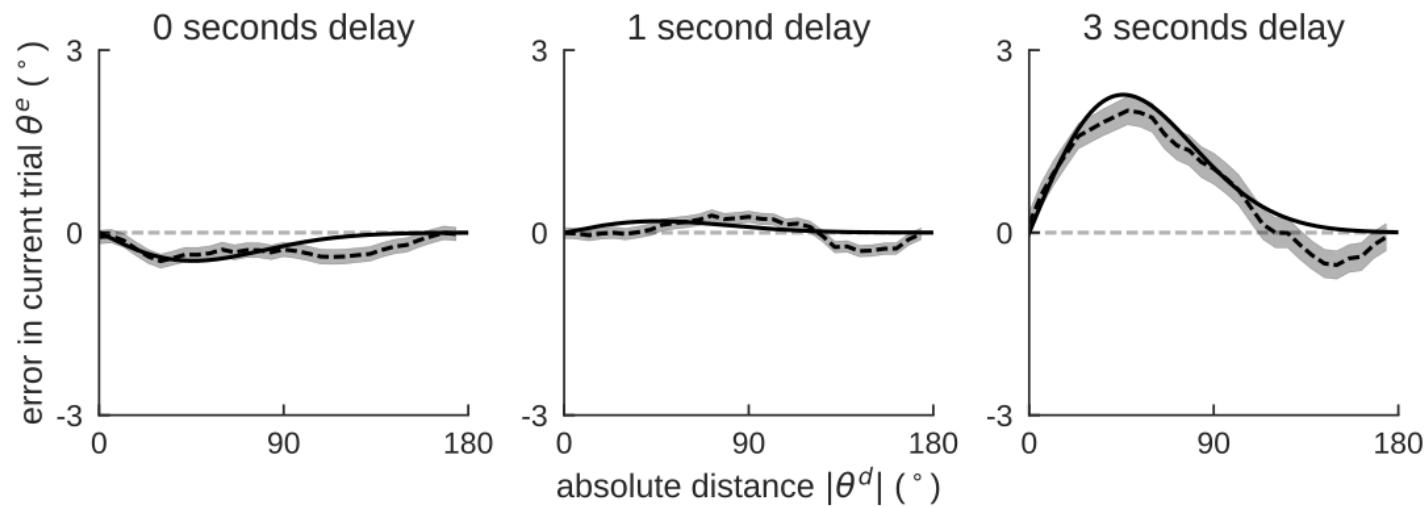
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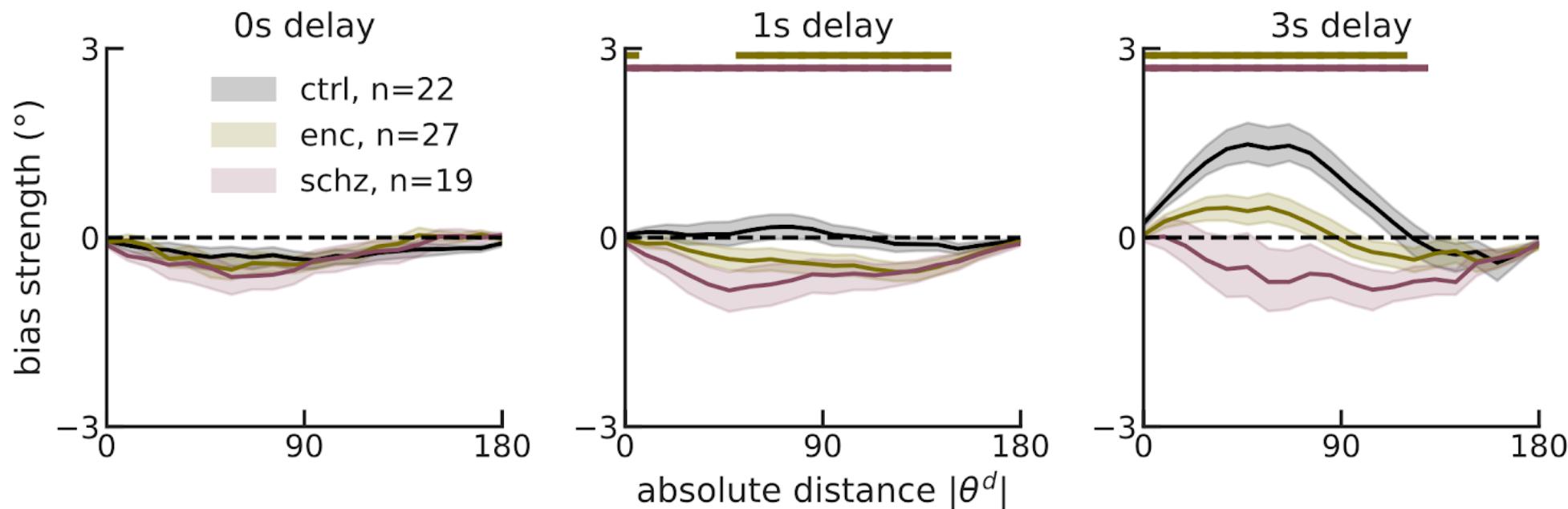
Attractive serial dependence is related to memory processes, as it emerges with delay



delay duration increases serial dependence, as already seen in:

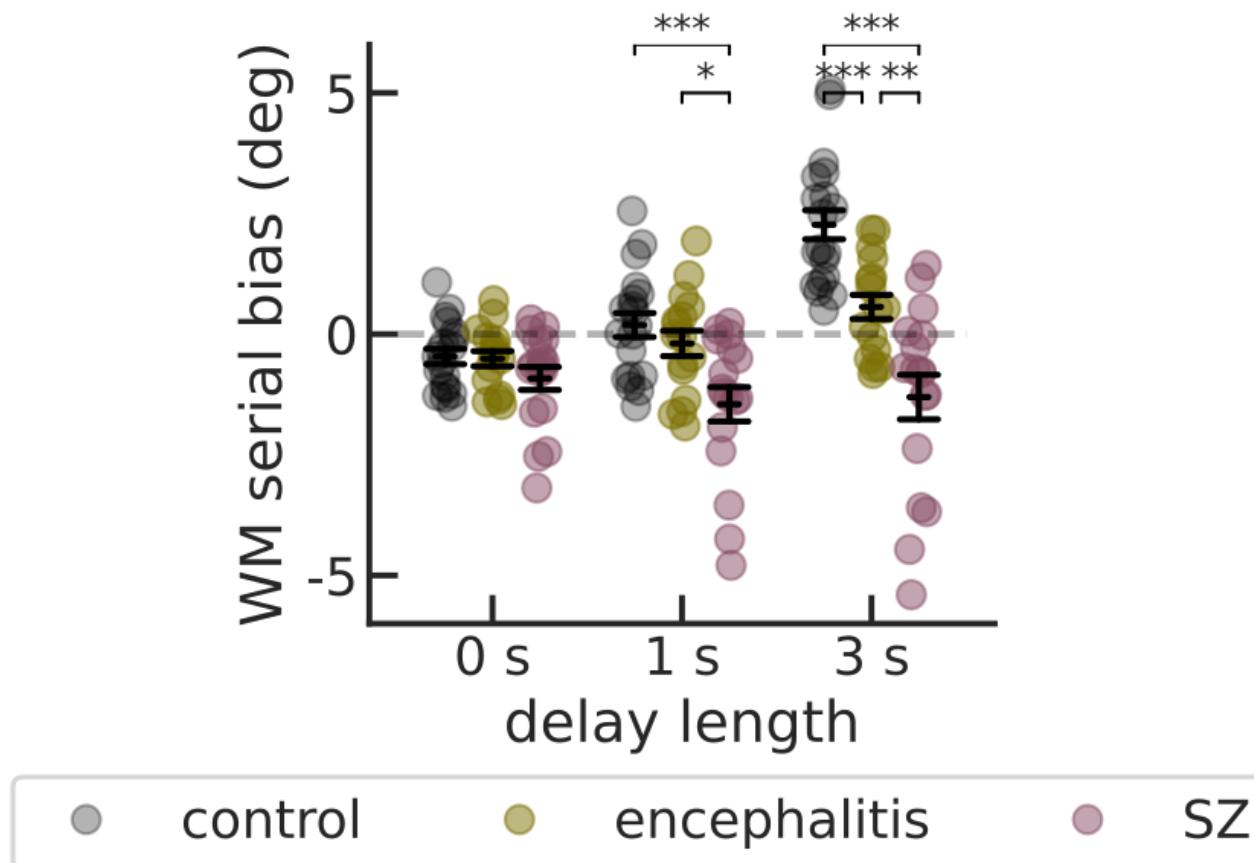
Fritzsche et al., *Curr Biol*, 2017
Bliss et al., *Sci Reports*, 2017

Attractive serial dependence is disrupted in encephalitis and schizophrenia



also in autism! but not in dyslexia (Lieder et al. Nat Neurosci 2019)

Attractive serial dependence is disrupted in encephalitis and schizophrenia

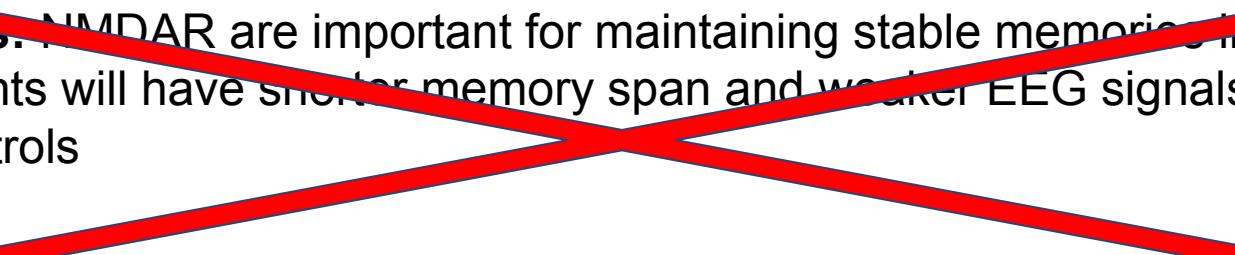


Objectives, questions, hypotheses

- Identify quantifiable behavioral deficits in spatial working memory in anti-NMDAR encephalitis and schizophrenia: **SERIAL DEPENDENCE**
 - Are there still analogies between anti-NMDAR encephalitis and schizophrenia following stabilization after acute periods? **YES**

(Stein*, Barbosa* et al. *Nat Commun* 2020)

Main hypothesis. NMDAR are important for maintaining stable memories in computational models, so patients will have shorter memory span and weaker EEG signals in memory periods than controls

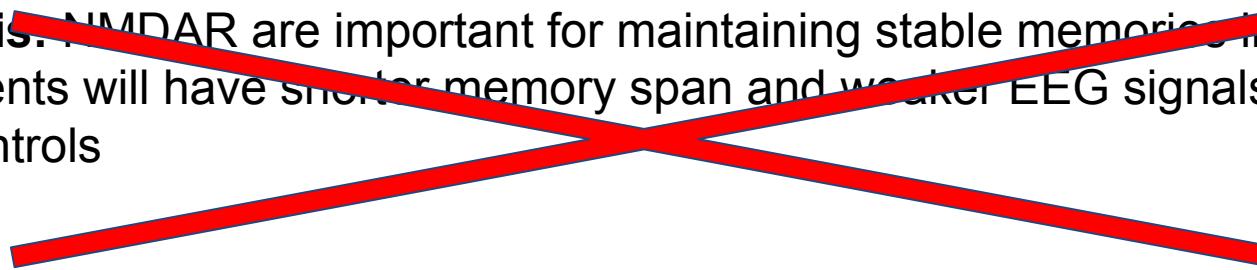


Objectives, questions, hypotheses

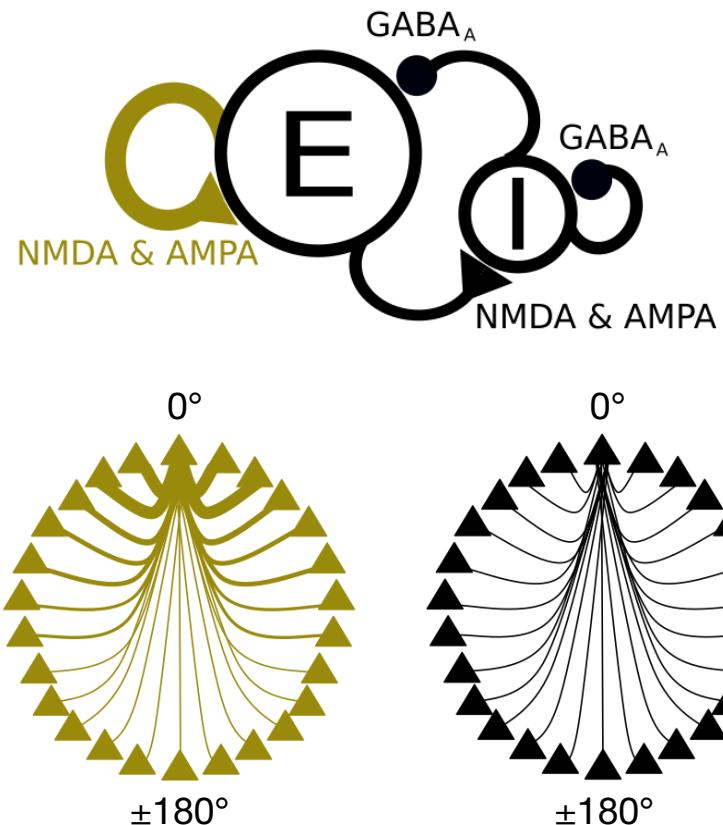
- Identify quantifiable behavioral deficits in spatial working memory in anti-NMDAR encephalitis and schizophrenia: **SERIAL DEPENDENCE**
 - Are there still analogies between anti-NMDAR encephalitis and schizophrenia following stabilization after acute periods? **YES**
- (Stein*, Barbosa* et al. *Nat Commun* 2020)
- **formulate plausible neural circuit alterations that give rise to the behavioral deficits, and their link to NMDARs**
 - **What is the main neural circuit alteration related to spatial working memory in the stabilized phase of the diseases?**

(Barbosa*, Stein* et al. *Nat Neurosci* 2020, unpublished)

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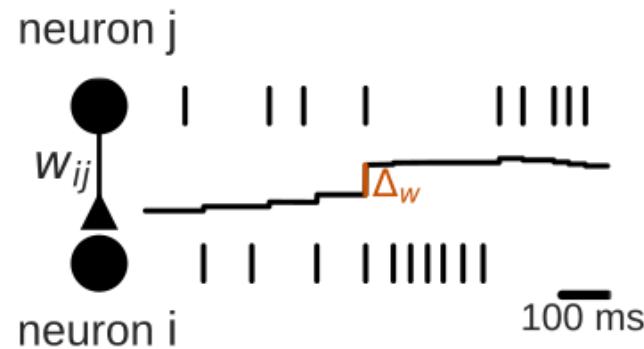


Working memory in a spiking neural network model of PFC

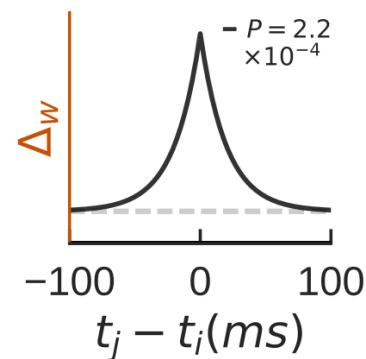


To explain inter-trial residual WM maintenance, we add a **short-term potentiation (STP)** mechanism at recurrent excitatory synapses

Working memory in a spiking neural network model of PFC



synaptic weights w_{ij} are enhanced in an **associative** fashion, depending on pre- and postsynaptic spike times t_j and t_i ,

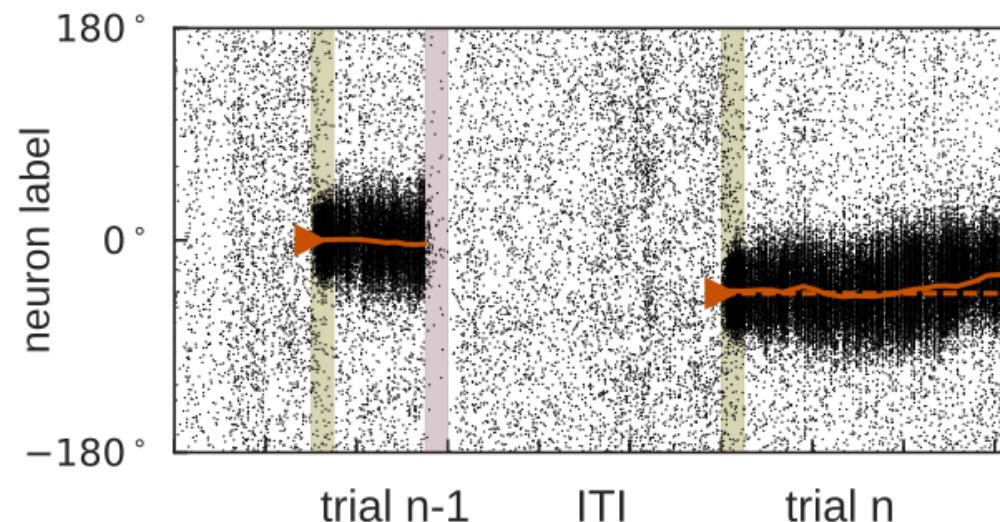


and decay with presynaptic spikes

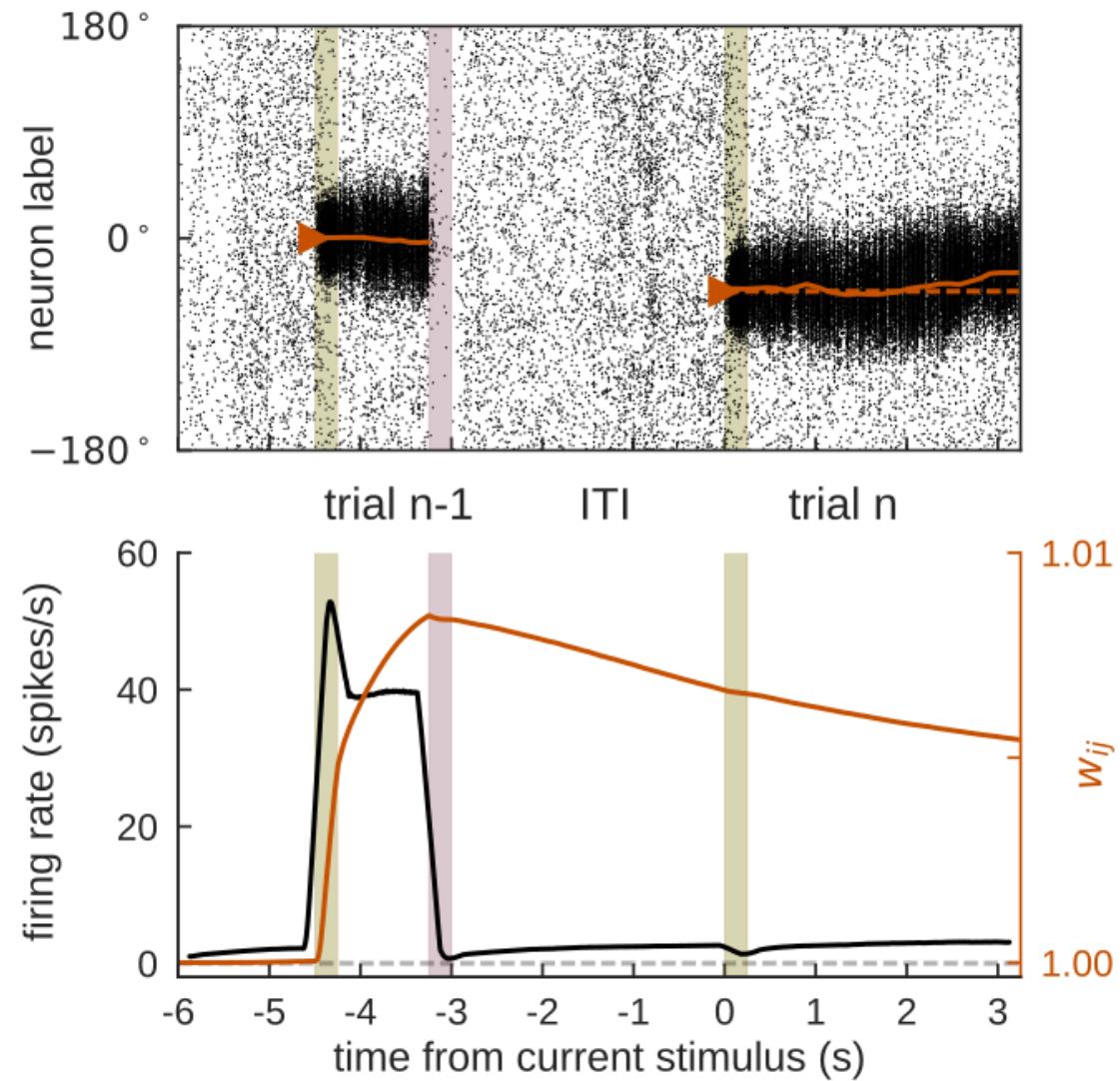
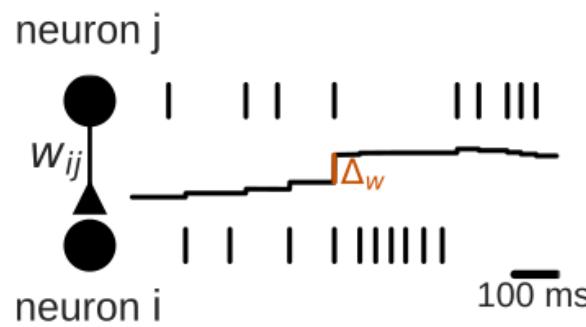
modeled after:

Volianskis et al., *J. Physiol*, 2013

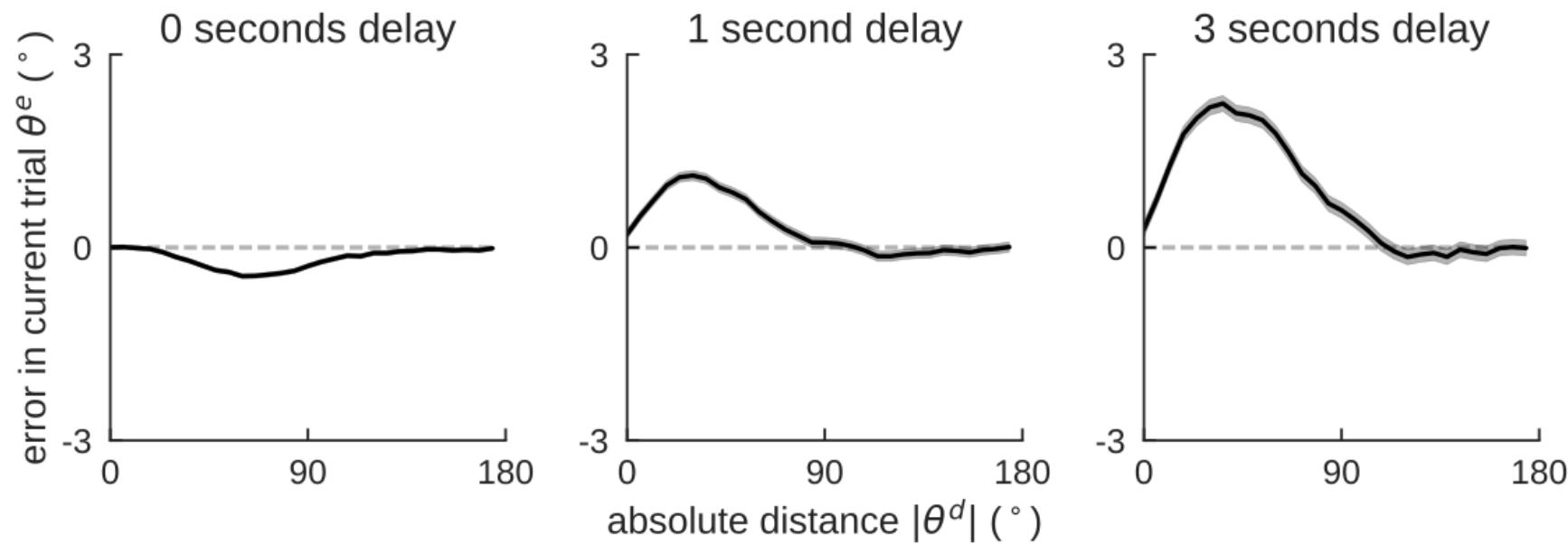
STP introduces attractive working memory biases



STP introduces attractive working memory biases

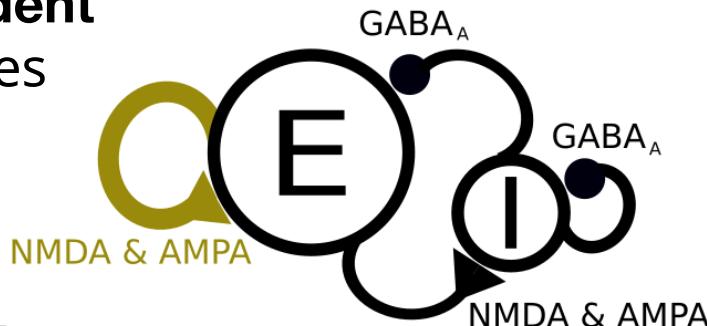


STP introduces attractive working memory biases



Which synaptic site is affected by NMDAR dysfunction?

3. ↓ NMDAR-dependent STP at E-E synapses

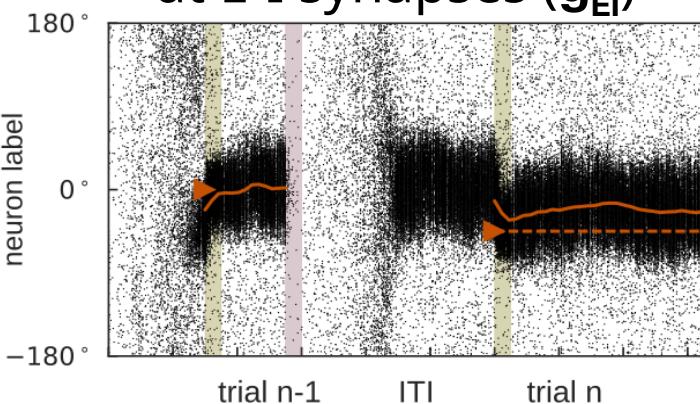


2. ↓ NMDAR-conductance
at E-E synapses (g_{EE})

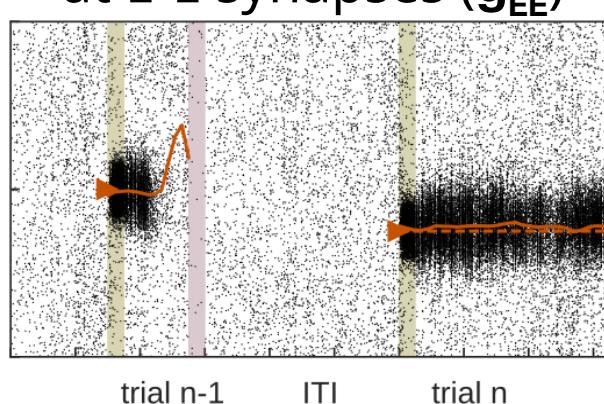
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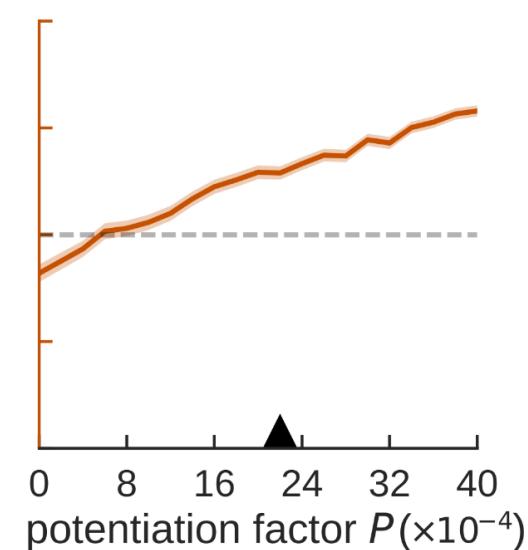
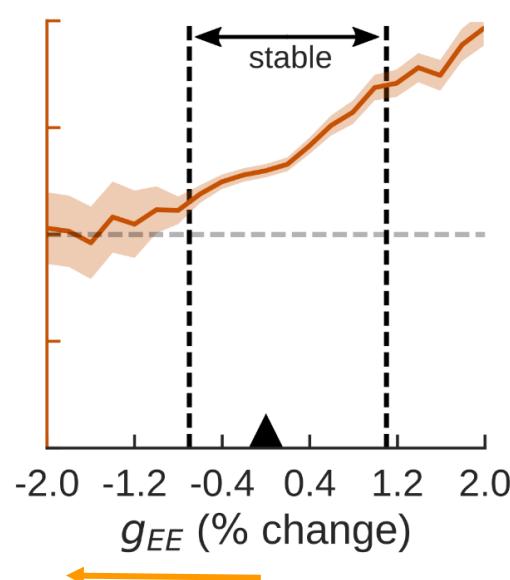
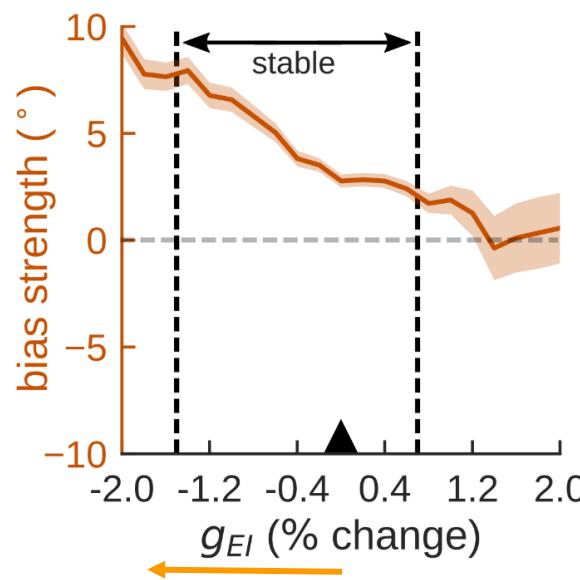
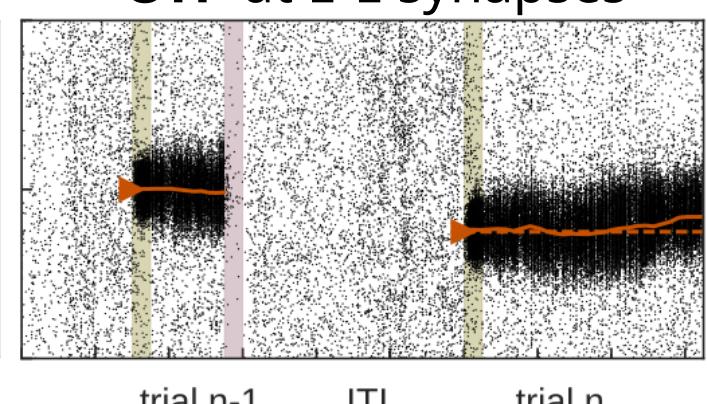
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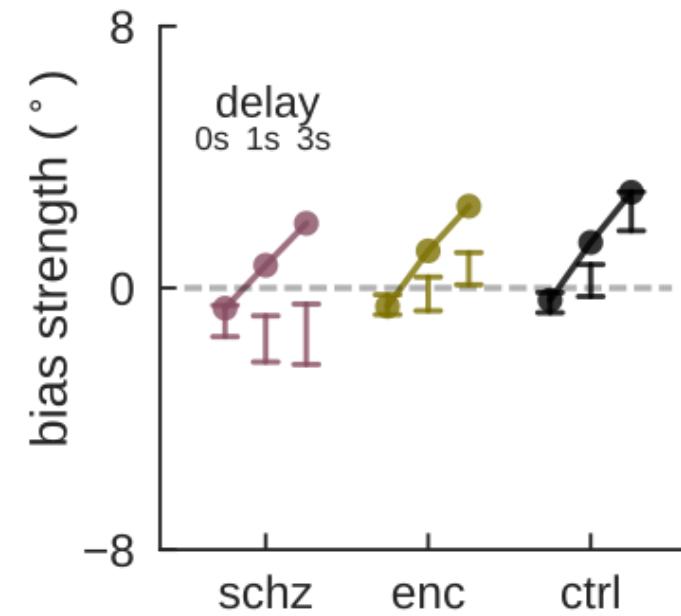
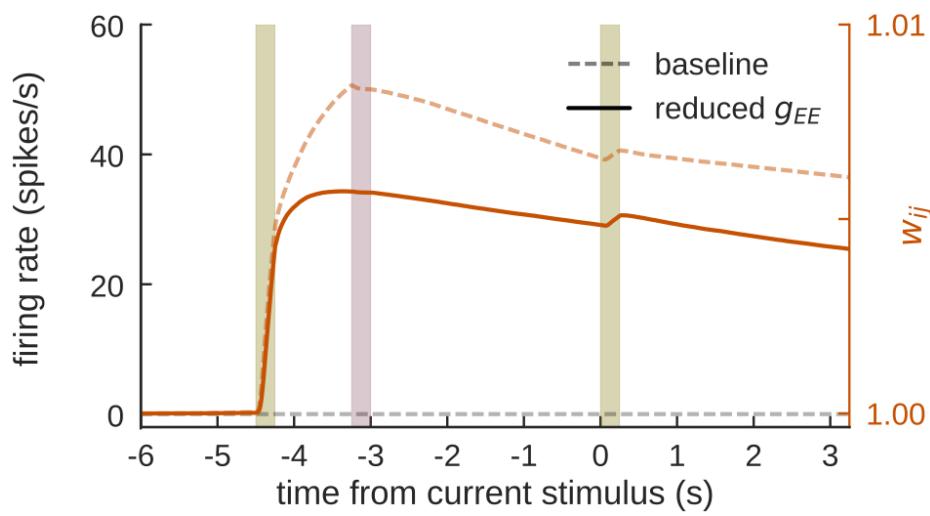
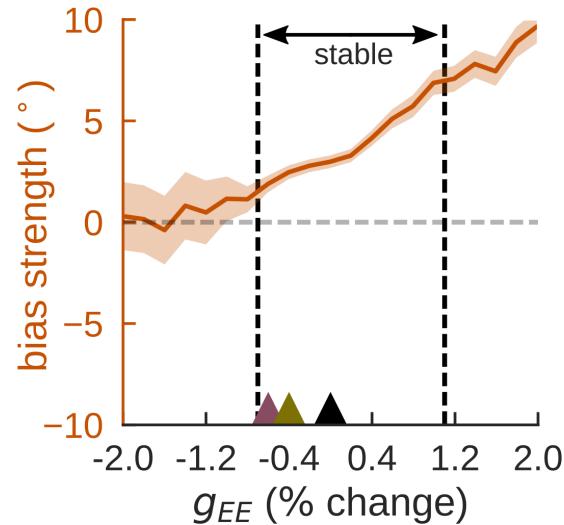
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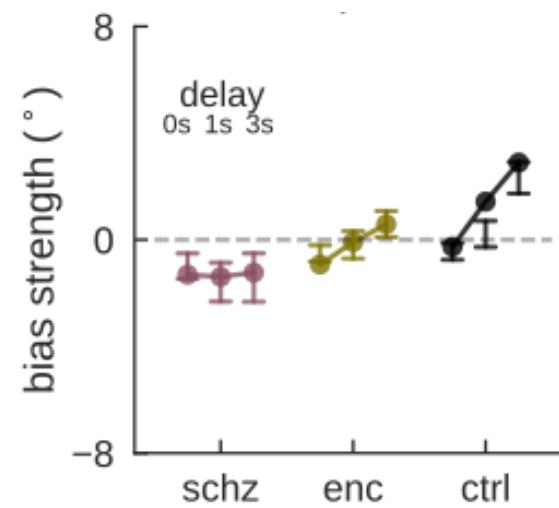
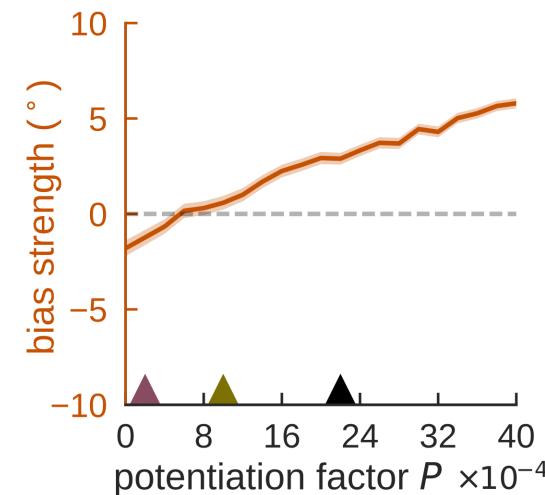
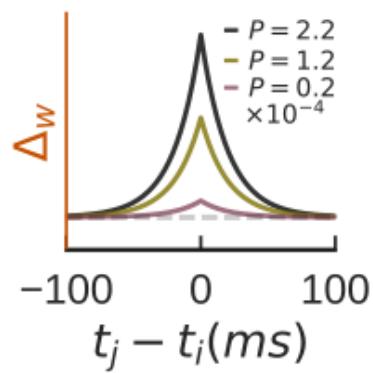
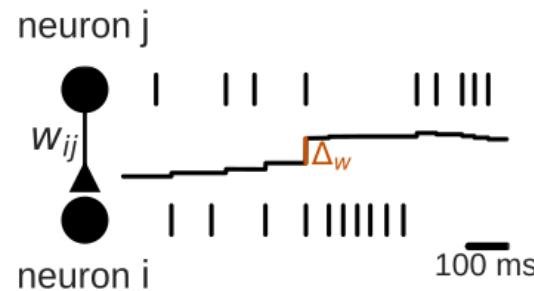
↓ NMDAR-dependent
STP at E-E synapses



Can $\downarrow g_{EE}$ disrupt delay-dependent biases?

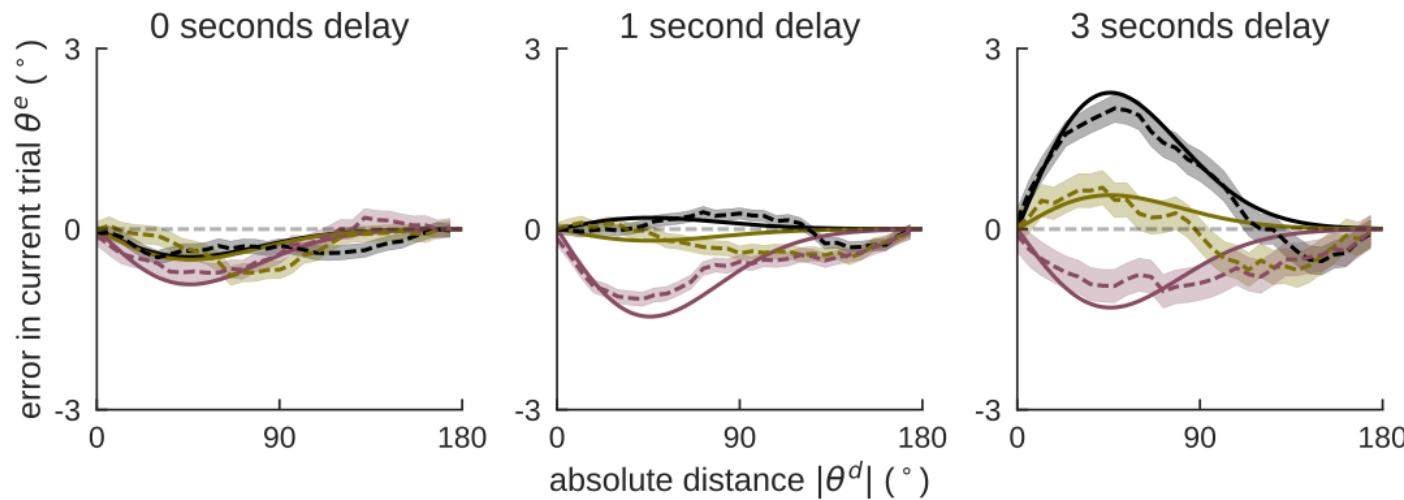


NMDAR-dependent STP affects serial dependence

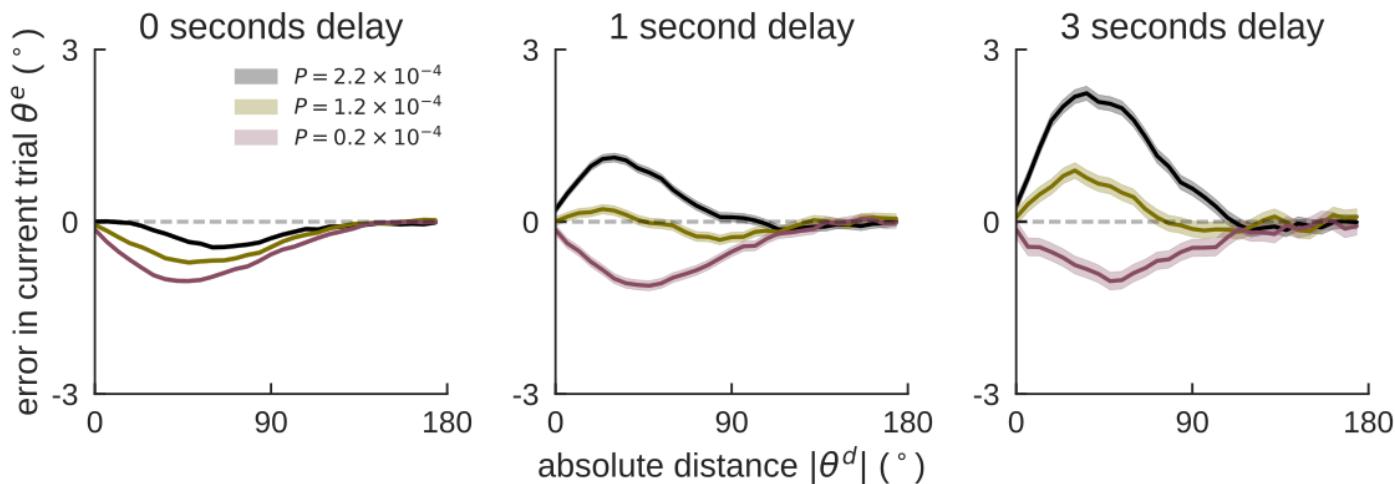


NMDAR-dependent STP affects serial dependence

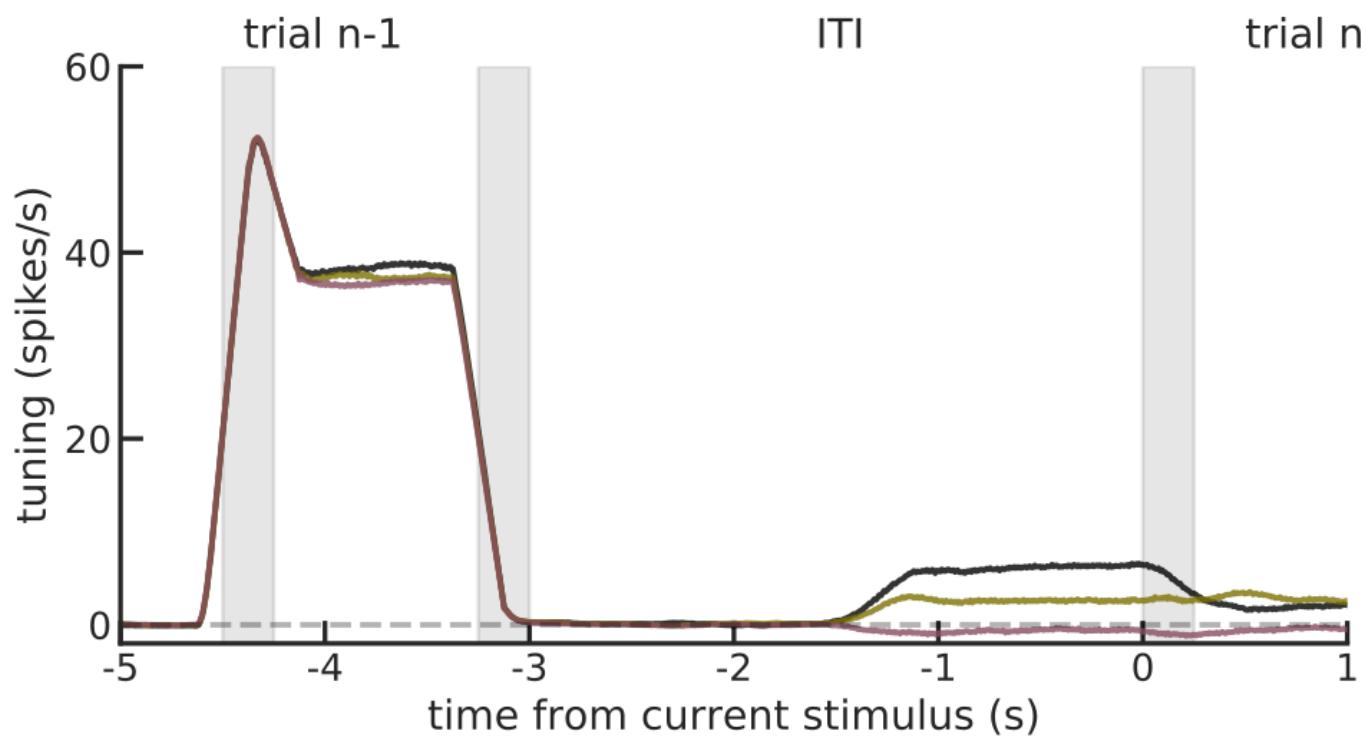
data



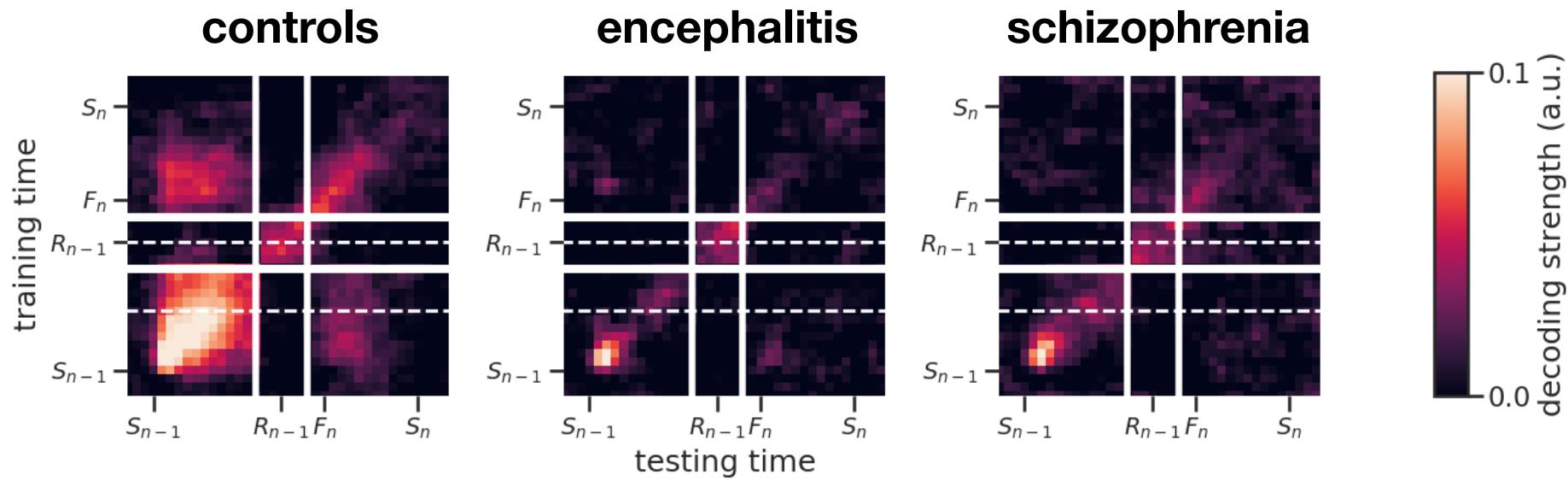
model



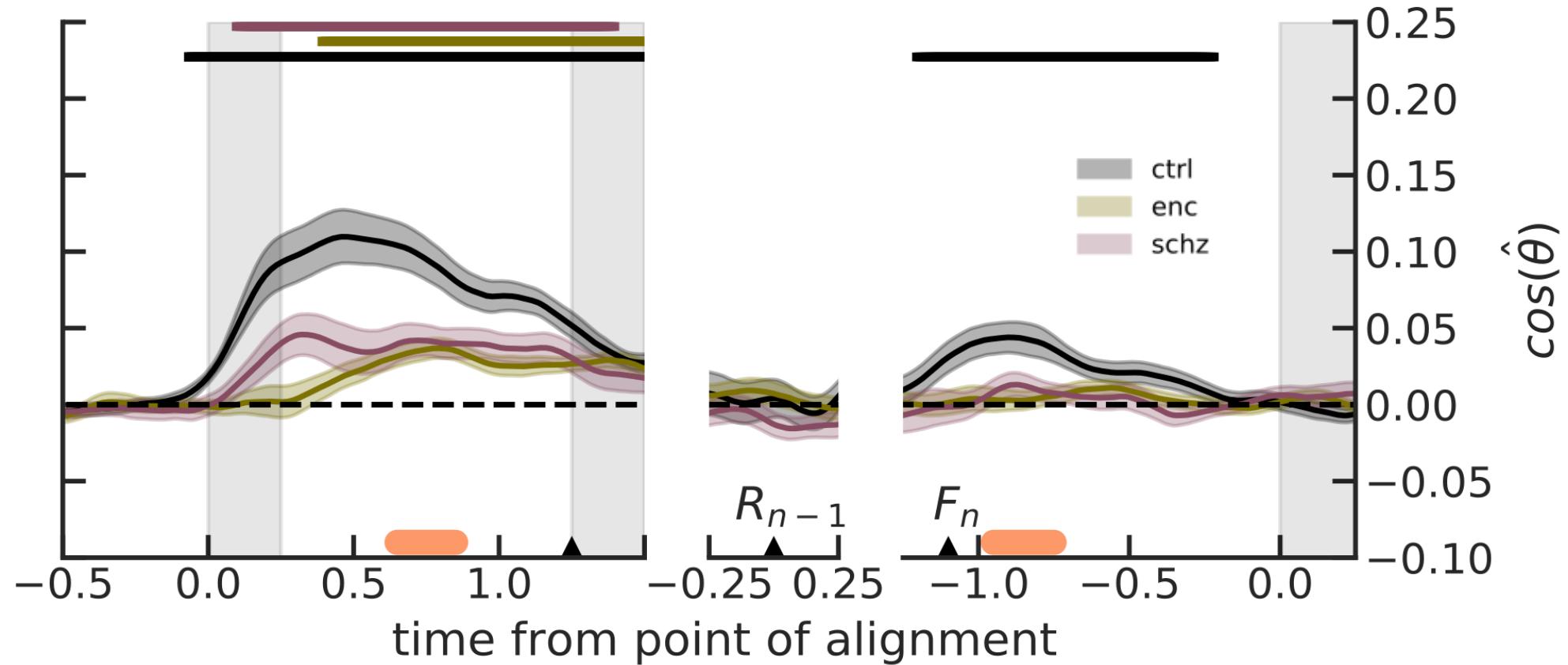
Physiological prediction: Reduced memory reactivation in patients



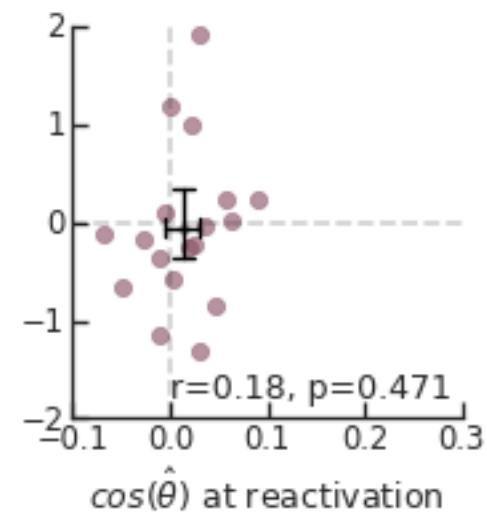
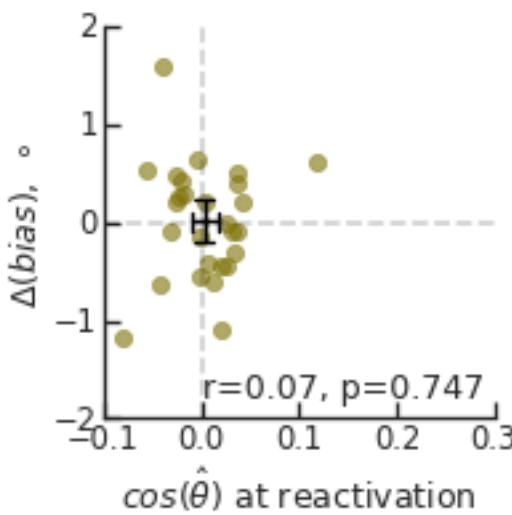
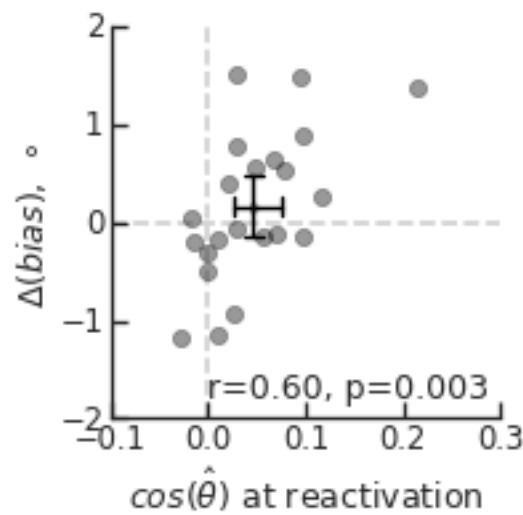
Patients' memory component generalizes less into the next trial



Patients' memory component does not reactivate in the fixation period



Memory reactivation in controls is related to serial dependence, but less so in patients



Conclusions

1. Behavioral working memory alterations in schizophrenia and anti-NMDAR encephalitis
reduced serial dependence with unaltered accuracy, consistent in both diseases
2. NMDAR dysfunction in a network model of working memory
reduced STP quantitatively fits behavioral results, E/I balance cannot fully explain findings
3. Neural signatures of altered working memory function
patients show weaker memory code and no fixation reactivation

Are cognitive deficits in anti-NMDAR encephalitis and schizophrenia related to slow plasticity mechanisms, rather than altered E-I imbalances?

Josefina Castro
IDIBAPS



Josep Dalmau
IDIBAPS, UPenn



Joan Santamaria
IDIBAPS



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Wake Forest Univ

