

Exploring cortical excitatory and inhibitory dysfunction in schizophrenia/psychosis using DCM

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Bogue Research Fellowships

Two major pathologies in Scz:

ΔExcitation/Inhibition in high hierarchical areas

- Genetics implicate NMDA-R & post-synaptic density
- ↓glutamatergic synapses in PFC & HC
- Many GABAergic markers diminished
- NMDAR antags/KO → ↓interneuron markers (e.g. GAD67, γ oscillations, etc)
- i.e. ?NMDAR-mediated loss of function of inhibitory interneurons and/or pyramidal cells

↑Striatal DAergic hyperactivity (esp at D₂Rs)

- All antipsychotics block D₂Rs
- ↑Presynaptic availability (and release) of DA
- Chronic amphetamine use causes psychosis

The excitatory/inhibitory imbalance hypothesis has some important issues:

- 1) It is underspecified
- 2) The mechanism is unclear
- 3) The dynamics are unclear
- 4) Are there subgroups?

The excitatory/inhibitory imbalance hypothesis has some important issues:

1) It is underspecified

Increased E/I?

=> loss of I? (too much E?)

2) The mechanism is unclear

3) The dynamics are unclear

Decreased E/I?

=> loss of E? (too much I?)

4) Are there subgroups?

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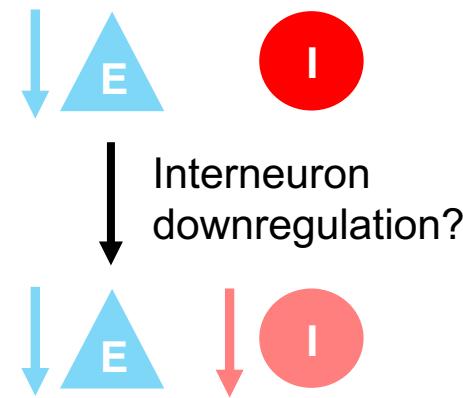
- 1) It is underspecified
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NMDA receptor dysfunction
could affect $E=I$, $E>I$ or $E<I$

PV interneurons may be
vulnerable to oxidative stress
(from environmental
stress/inflammation)

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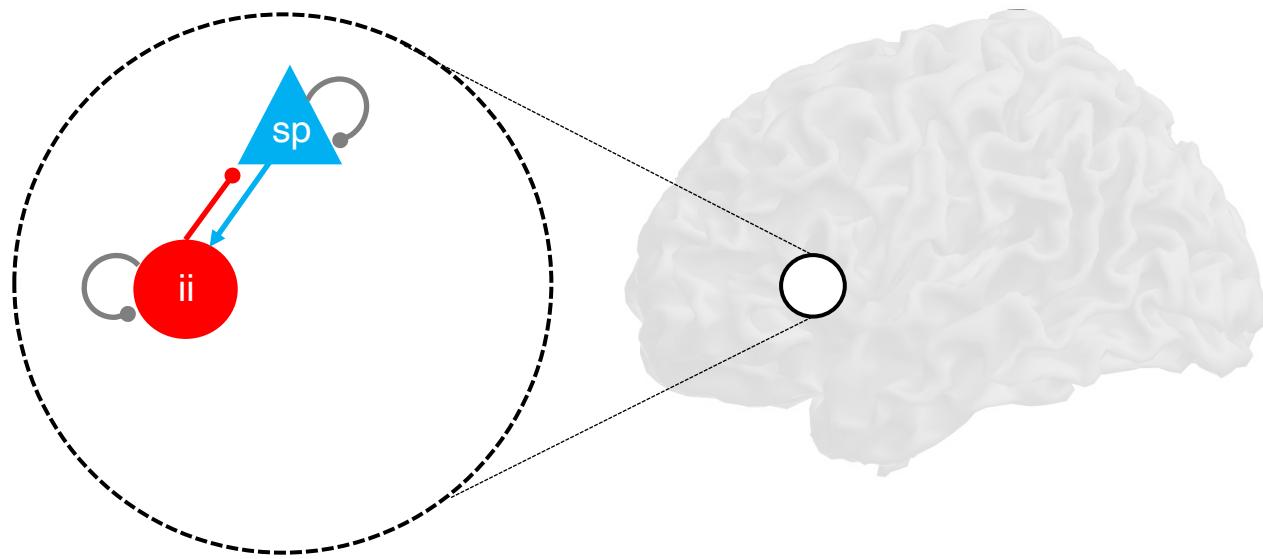
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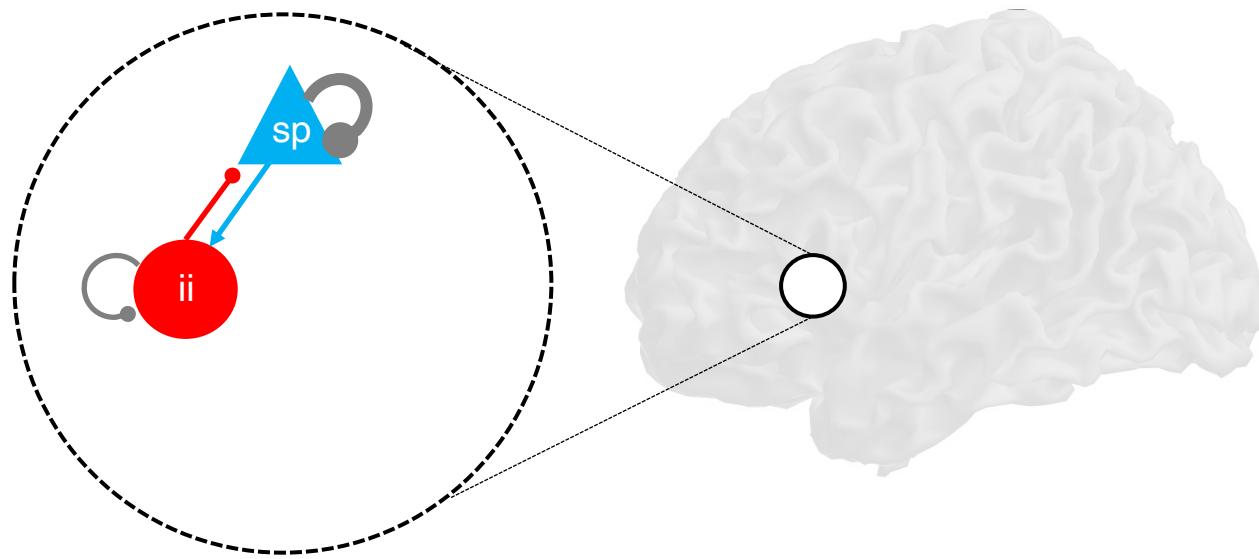


...all have key implications for treatments

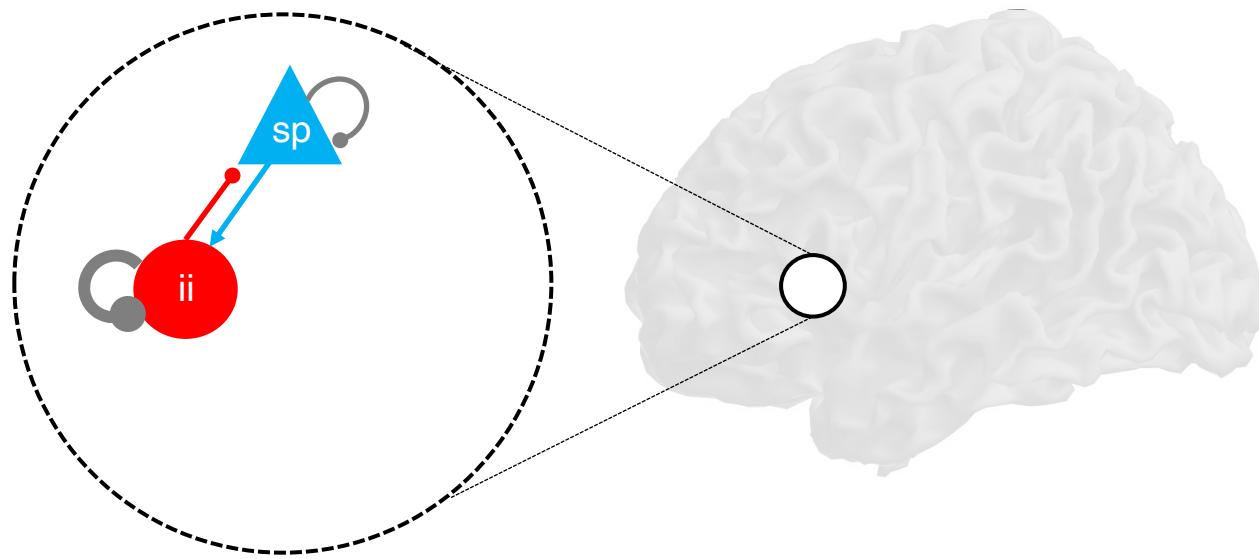
What is the nature of excitatory and inhibitory changes in schizophrenia?



What is the nature of excitatory and inhibitory changes in schizophrenia?
Loss of pyramidal cell excitability?

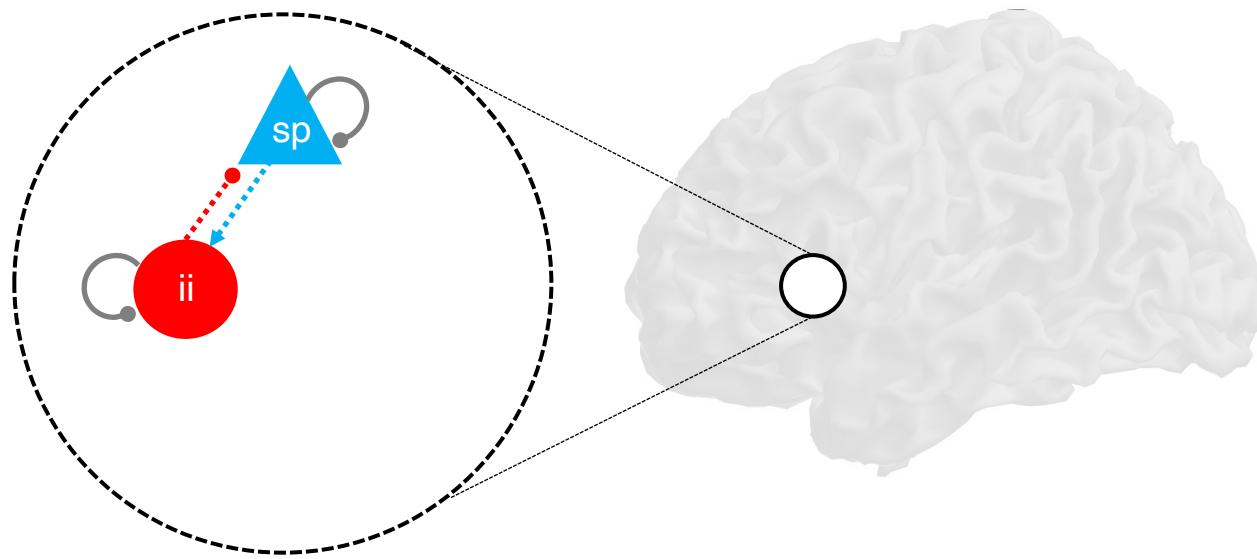


What is the nature of excitatory and inhibitory changes in schizophrenia?
Loss of inhibitory interneuron excitability?

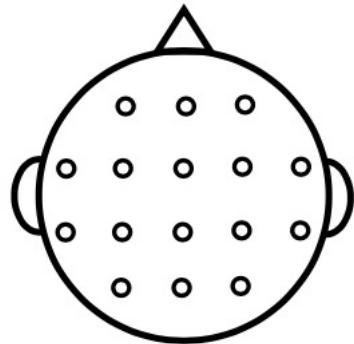


What is the nature of excitatory and inhibitory changes in schizophrenia?

Loss of connectivity between pyramidal cells and interneurons?

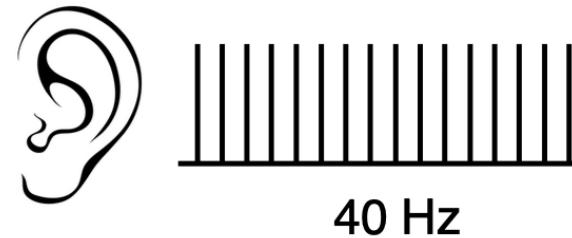


Maryland data: 107 Con & 108 Scz (age 39 ± 14 yrs, ~2/3 male, ~1/3 smokers),
 57 Rel (age 45 ± 16 yrs, ~2/3 female, ~1/6 smokers)



Con n=98
 Scz n=95
 Rel n=0

rsEEG



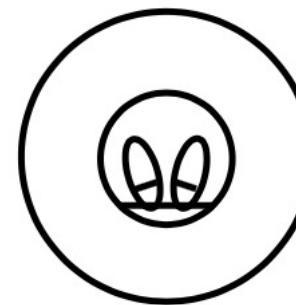
Con n=92
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EEG ASSR 40 Hz



Con n=93
 Scz n=95
 Rel n=40

EEG MMN



Con n=85
 Scz n=72
 Rel n=45

rsfMRI

Key questions for a cross-modality modelling analysis:

- 1) Are there consistent changes in model parameters in Scz across paradigms?
- 2) Do these changes relate to synaptic gain?
- 3) Do they relate to symptoms in Scz?

Dynamic causal modelling approach

Forward model (measurement)

$$y = g(x, \theta) + \varepsilon$$

Observed data

$$p(y | x, \theta, u, m)$$

Model inversion

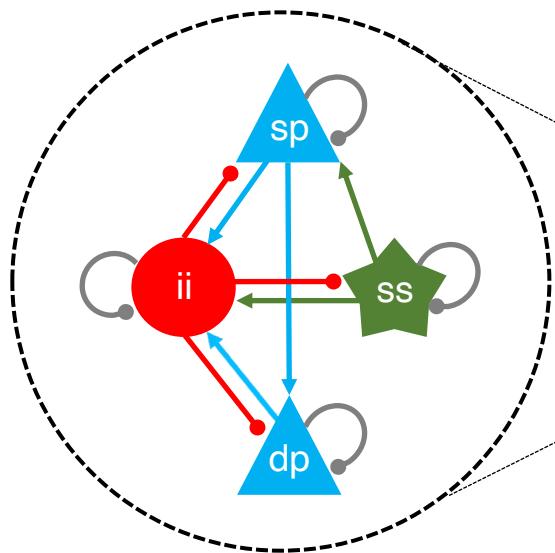
$$p(x, \theta | y, u, m)$$

Forward model (neuronal)

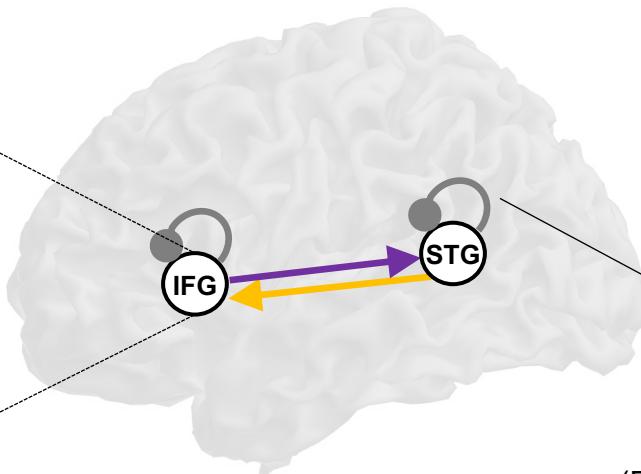
$$\dot{x} = f(x, u, \theta) + \omega$$



Dynamic causal modelling approach



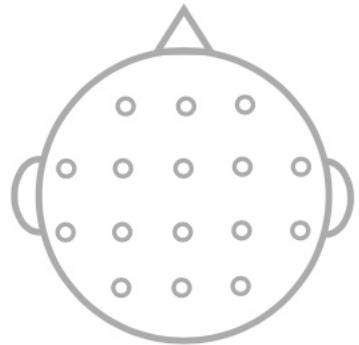
Canonical microcircuit model
(EEG only): all connections



2 area model (example)

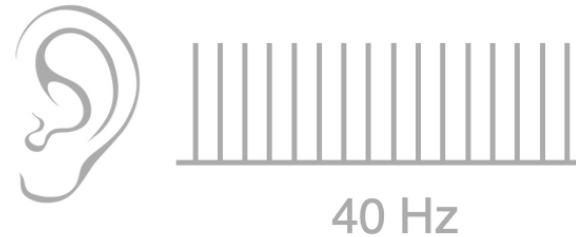
self-inhibitory connection
(EEG: 'excitability' of
sp cells in microcircuit)

Resting state EEG



Con n=98
Scz n=95
Rel n=0

rsEEG



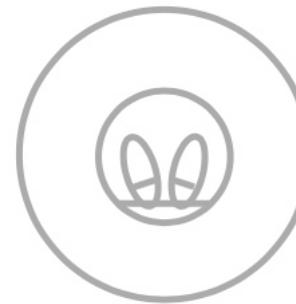
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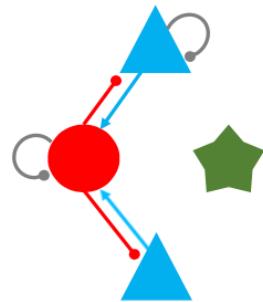
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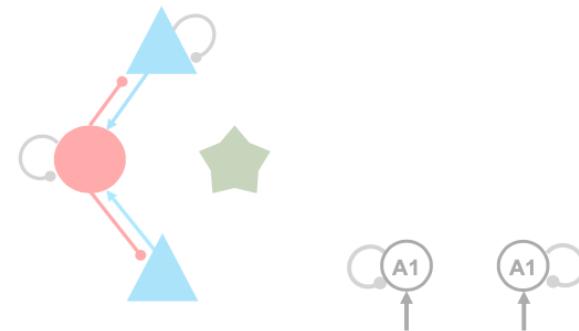
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rsfMRI

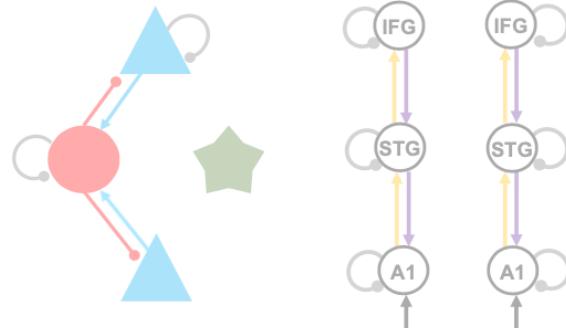
Resting state EEG



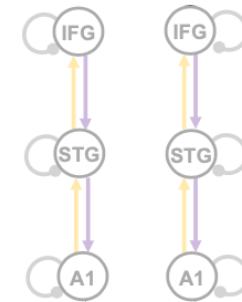
rsEEG – DCM for CSD



EEG ASSR 40 Hz – DCM for CSD



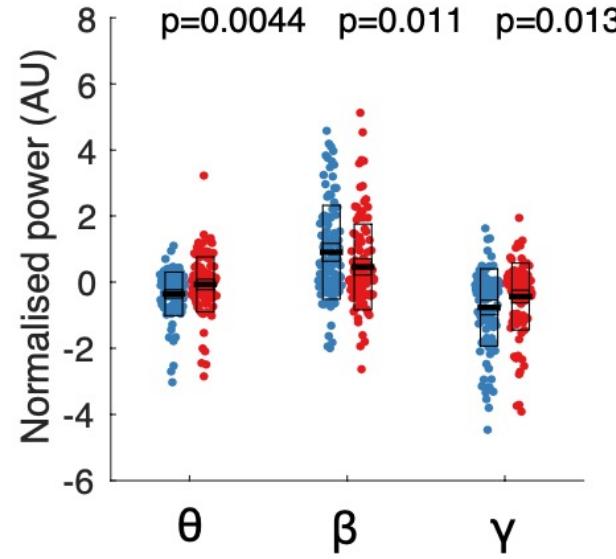
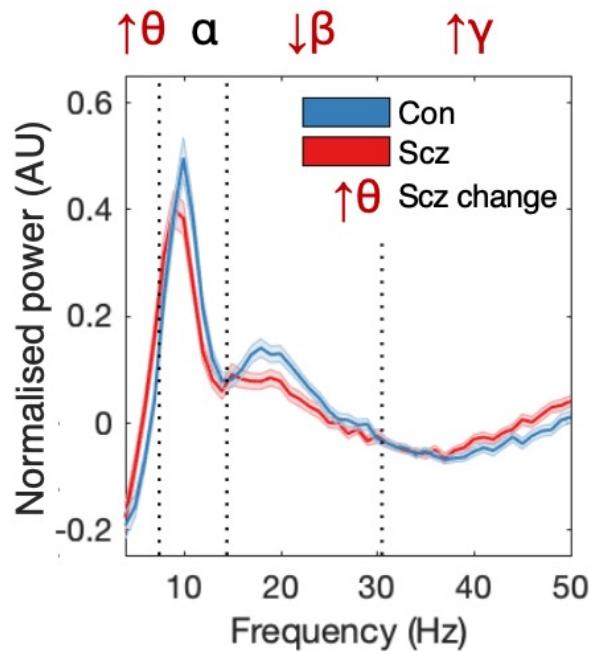
EEG MMN – DCM for ERP



rsfMRI – spectral DCM

Resting state EEG in Scz vs controls (n=207) shows $\uparrow\theta$ & γ , $\downarrow\beta$ and $\leftrightarrow\alpha$

rsEEG: eyes open

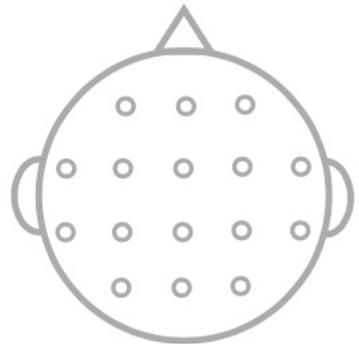


Can we use DCM to simulate resting state EEG in Scz: $\uparrow\theta$ & γ , $\downarrow\beta$?

- Con simulations
- Scz simulations (<30% change in parameters)

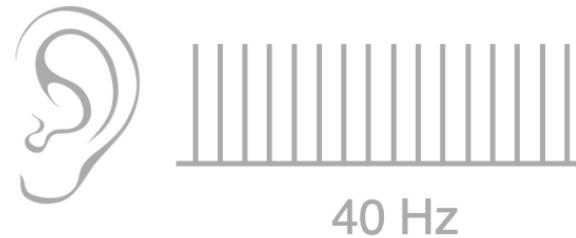
- $\uparrow\theta$ Simulation matches Scz rsEEG
- $\uparrow\theta$ Simulation doesn't match Scz rsEEG

Mismatch negativity



Con n=98
Scz n=95
Rel n=0

rsEEG

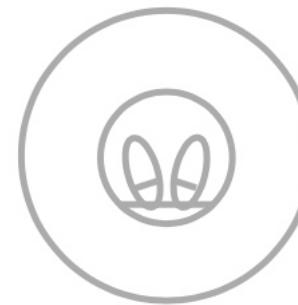


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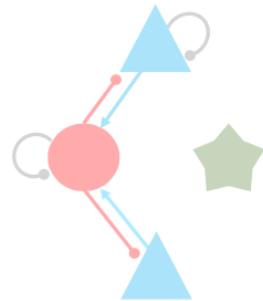
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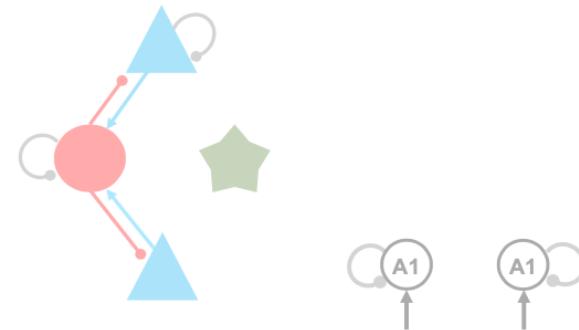
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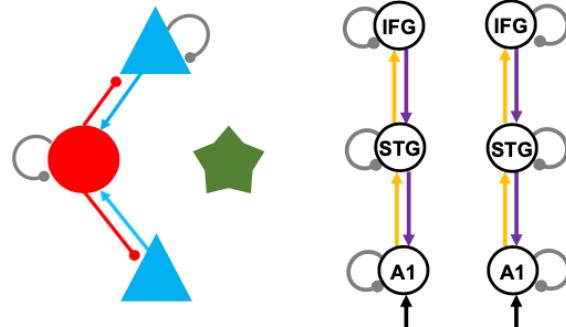
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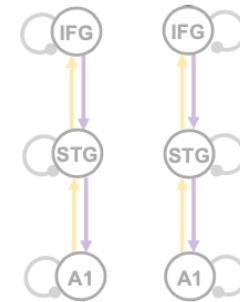
rsEEG – DCM for CSD



EEG ASSR 40 Hz – DCM for CSD



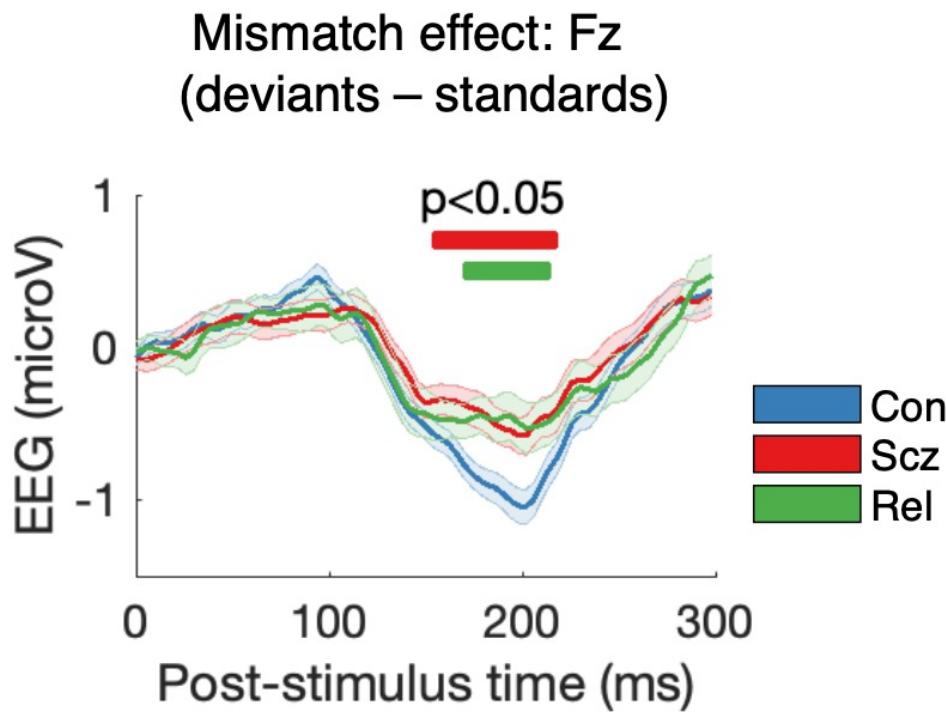
EEG MMN – DCM for ERP



rsfMRI – spectral DCM

Mismatch negativity

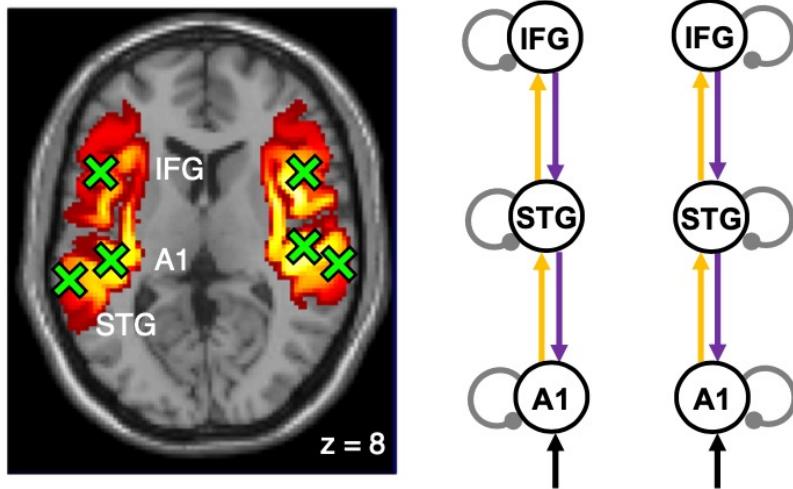
MMN EEG dataset (94 Con, 96 Scz, 42 Rel) reveals classic loss of ‘surprise’ signal to deviant stimuli in Scz & Rel



Mismatch negativity

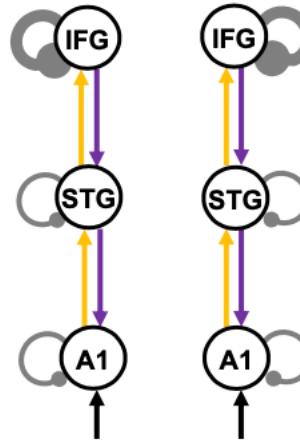
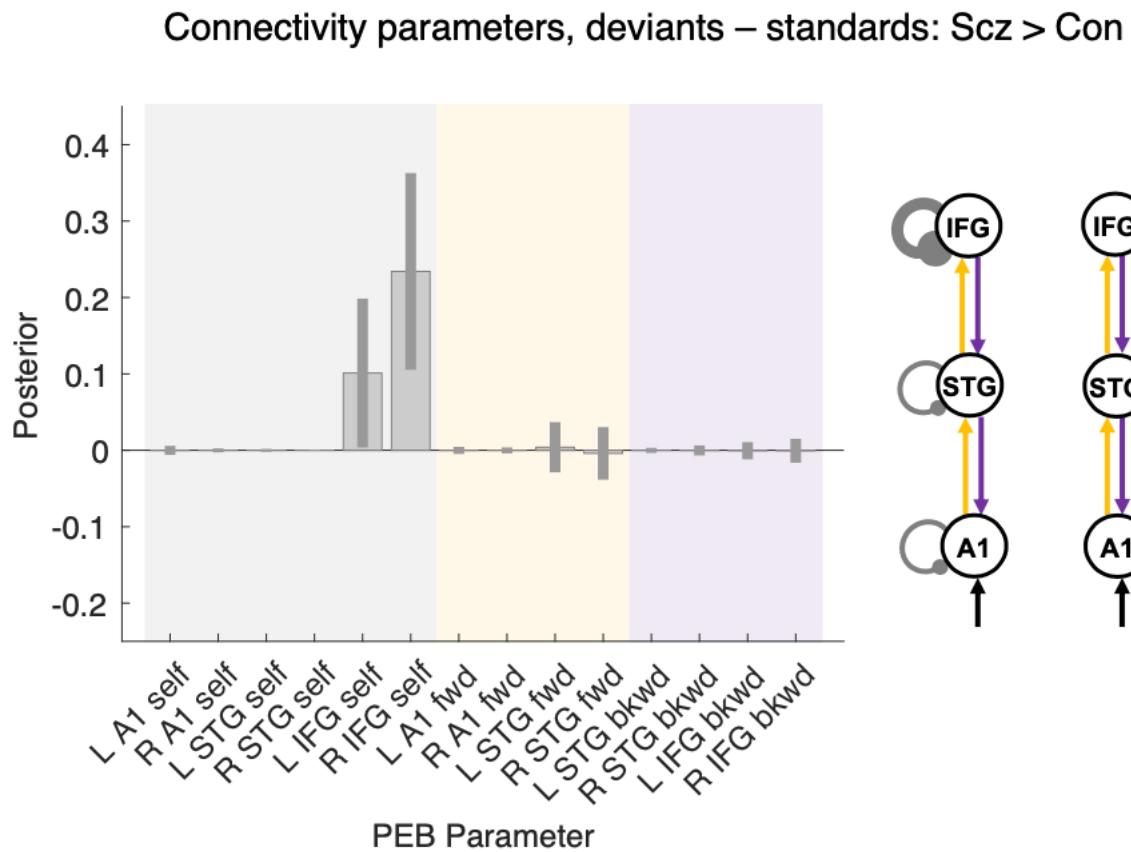
MMN sources and model structure are well-established:

MMN sources and model structure



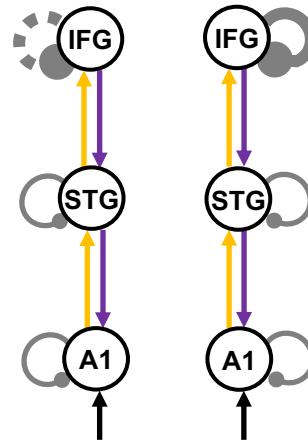
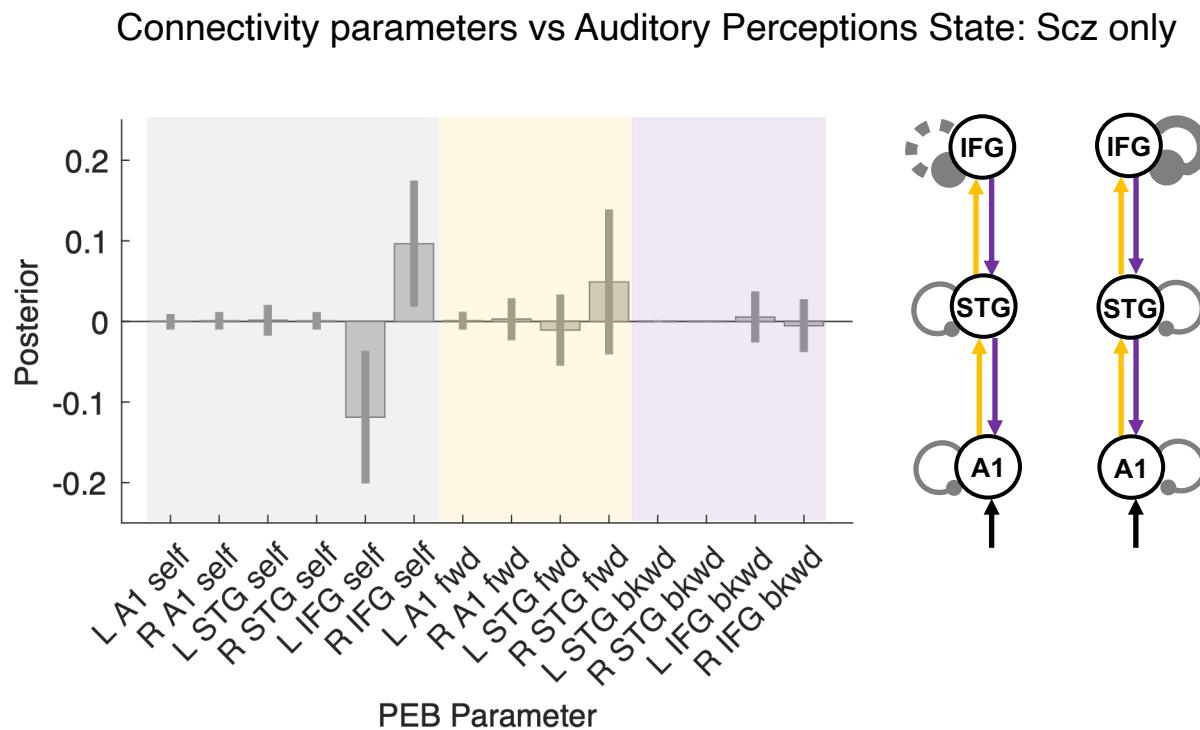
Mismatch negativity

Loss of mismatch negativity in Scz relates to loss of gain in IFG

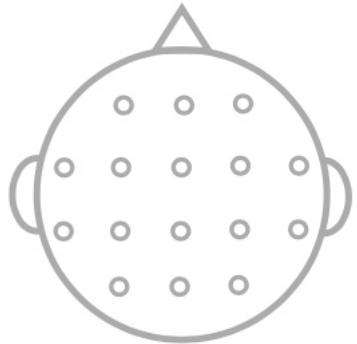


Mismatch negativity

Abnormal auditory percepts in Scz assoc w mismatch-related *disinhibition* in L IFG (i.e. BA44, or Broca's area), as well as the group effect of decreased gain in R IFG

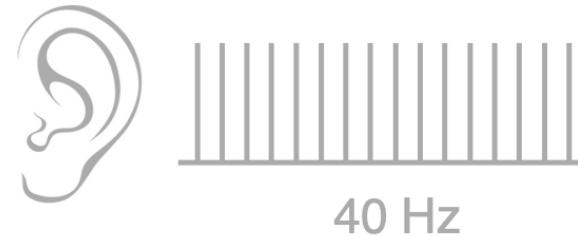


40 Hz auditory steady state response



Con n=98
Scz n=95
Rel n=0

rsEEG



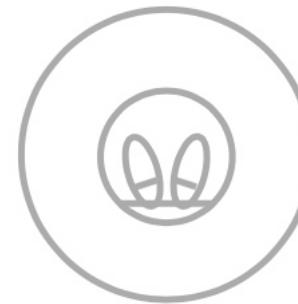
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EEG ASSR 40 Hz



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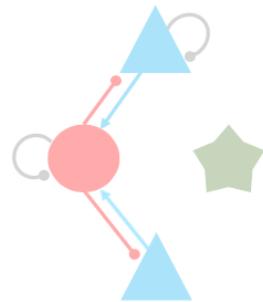
EEG MMN



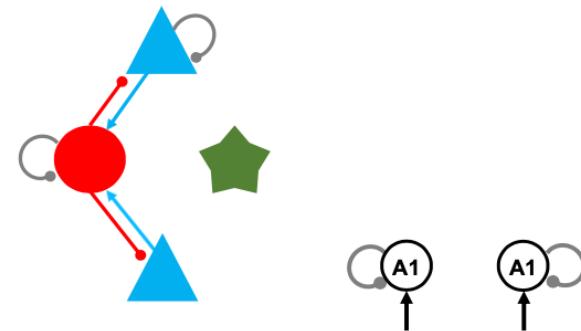
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rsfMRI

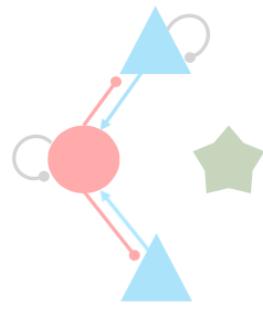
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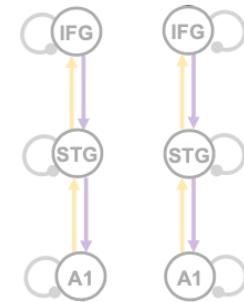
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EEG ASSR 40 Hz – DCM for CSD



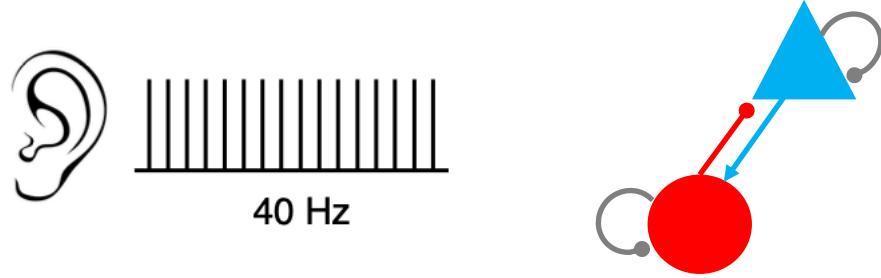
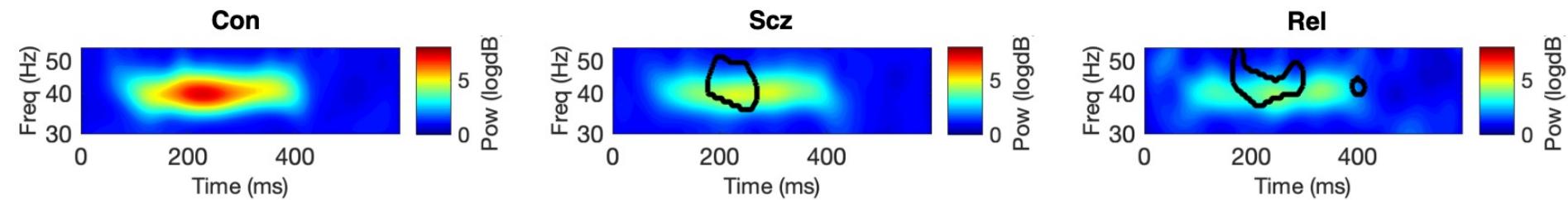
EEG MMN – DCM for ERP



rsfMRI – spectral DCM

40 Hz auditory steady state response

Auditory steady state response to 40 Hz clicks (92 Con, 94 Scz, 42 Rel) reveals loss of 40 Hz power in Scz and Rel



40 Hz auditory steady state response



Scz & Rel share a loss of pyramidal input into interneurons,
but Scz also have a loss of gain in bilateral A1

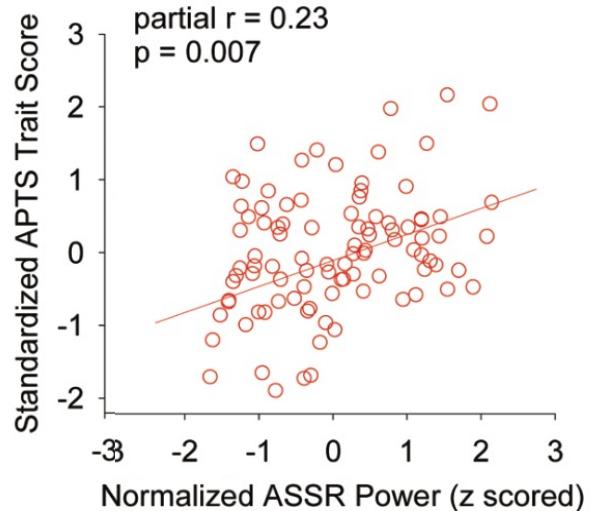
ASSR microcircuit parameters: Scz+Rel > Con

ASSR microcircuit parameters: Scz > Rel

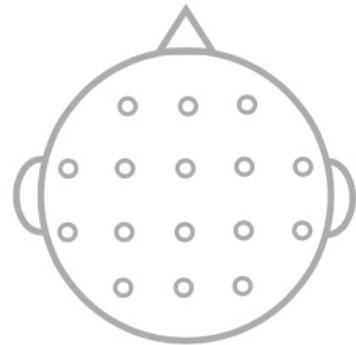
40 Hz auditory steady state response

Abnormal auditory perceptions in Scz relate to disinhibition of sup pyr cells
– this fits with their +ve relationship with 40 Hz ASSR power

ASSR parameters vs Auditory Perceptions Trait: Scz only

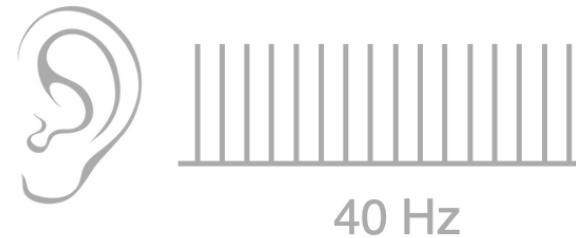


Resting state fMRI



Con n=98
Scz n=95
Rel n=0

rsEEG



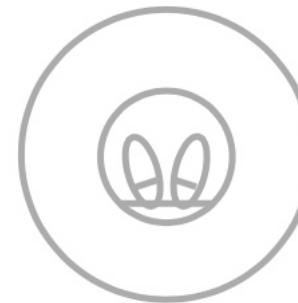
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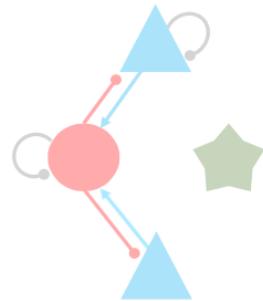
EEG MMN



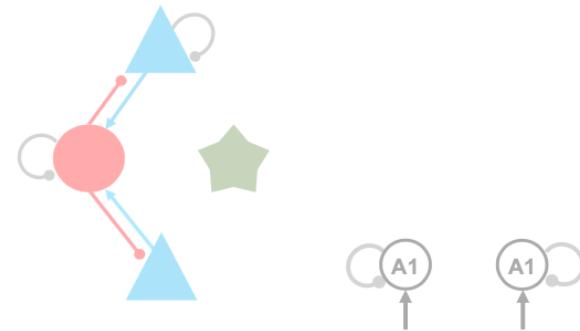
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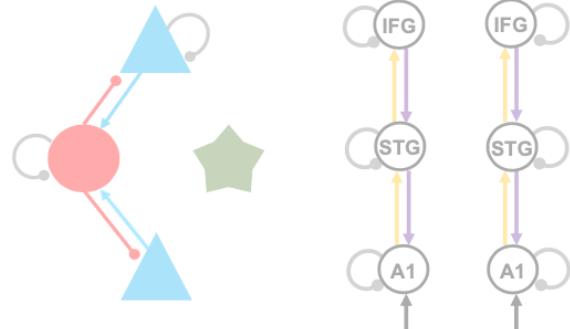
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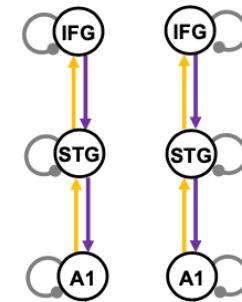
rsEEG – DCM for CSD



EEG ASSR 40 Hz – DCM for CSD



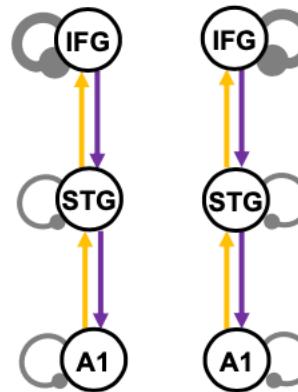
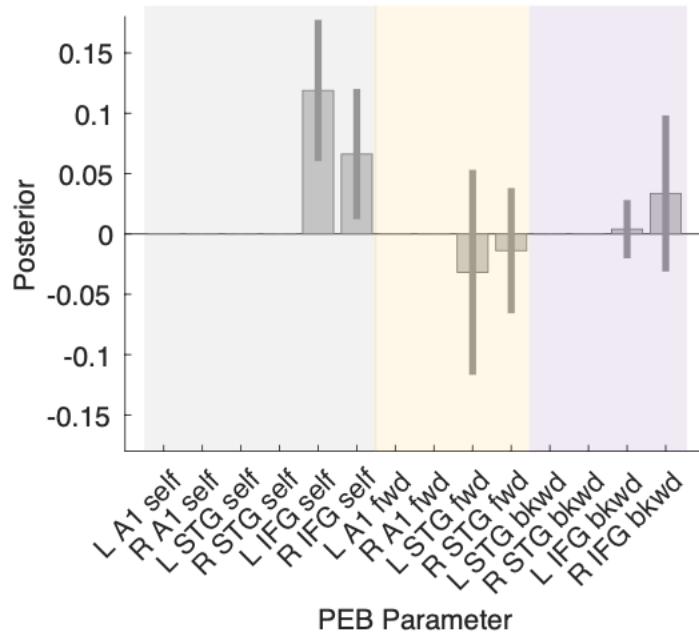
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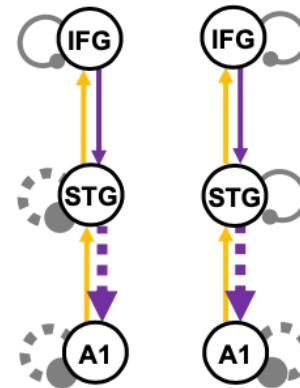
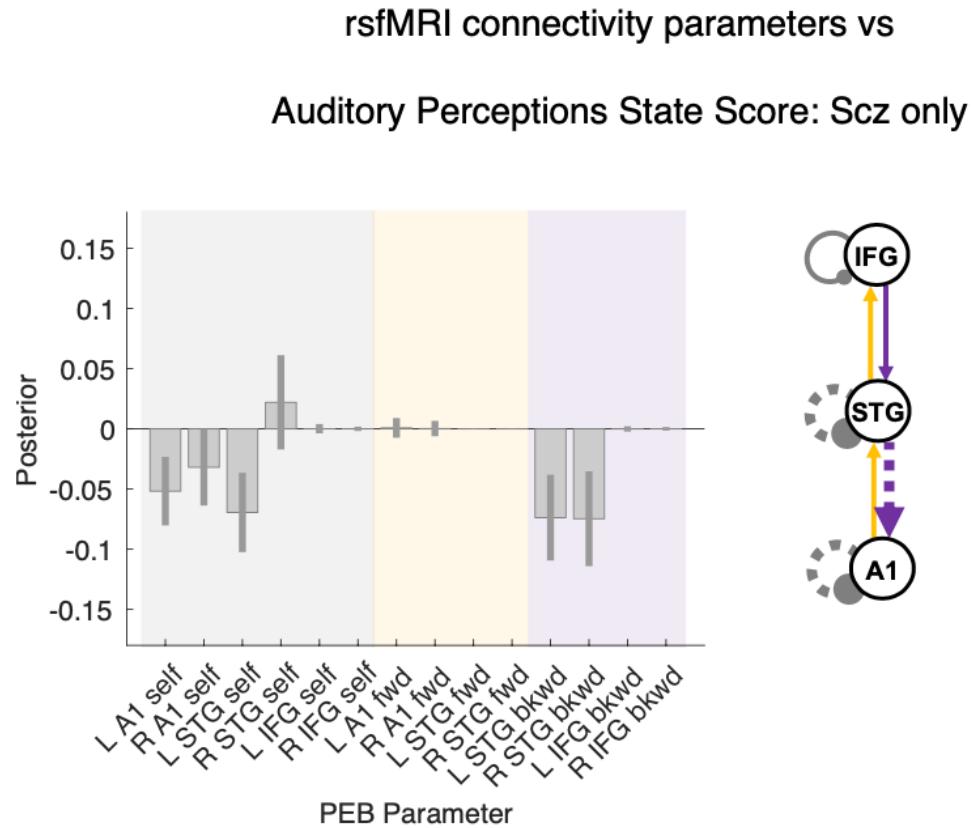
rsfMRI – spectral DCM

In rsfMRI, Scz again show loss of excitability in bilateral frontal areas

rsfMRI connectivity parameters: Scz > Con

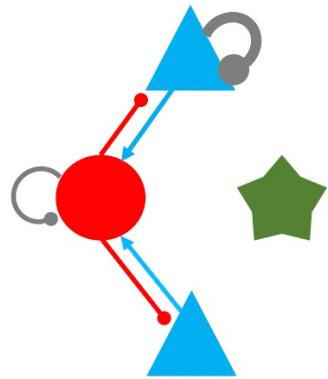


In rsfMRI, Scz abnormal auditory perceptions relate to auditory cortical *disinhibition*

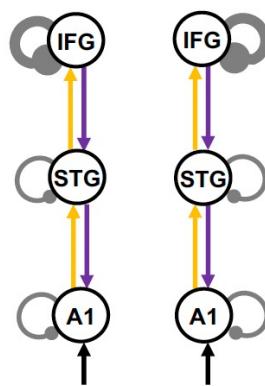


Cross-paradigm findings

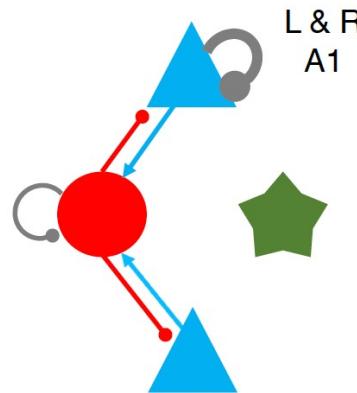
Summary: there are some striking consistencies across paradigms –
Loss of excitability in Scz, especially in frontal areas



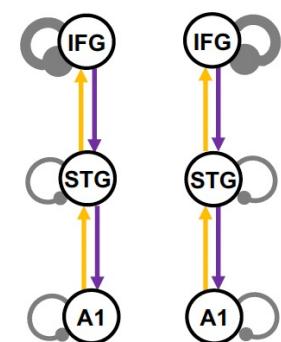
Scz simulations, rsEEG



Scz > Con, MMN



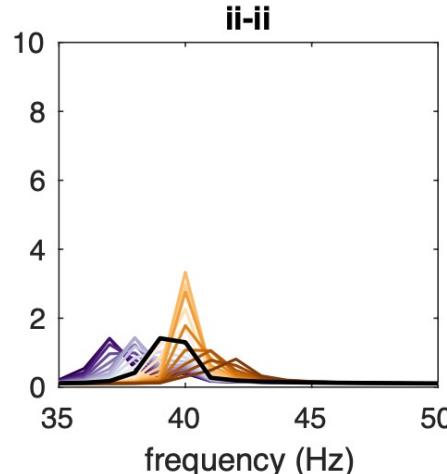
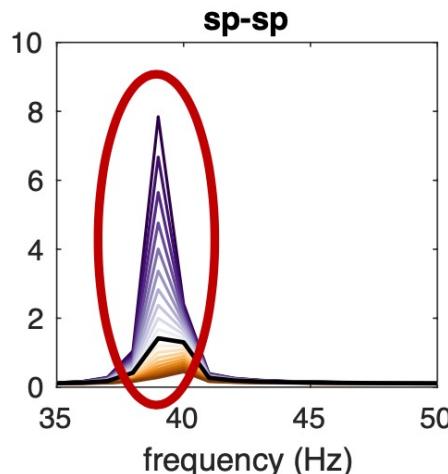
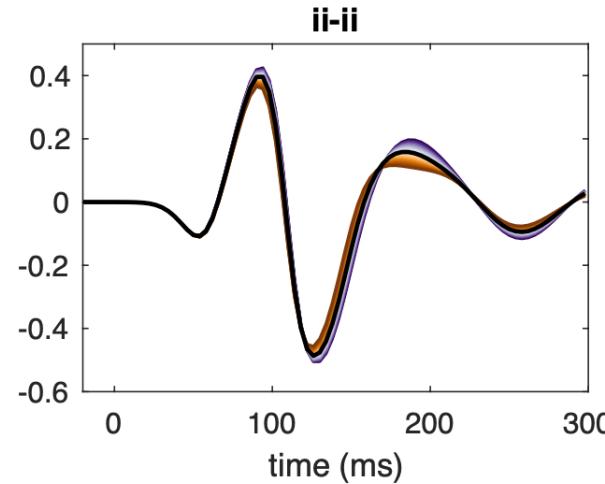
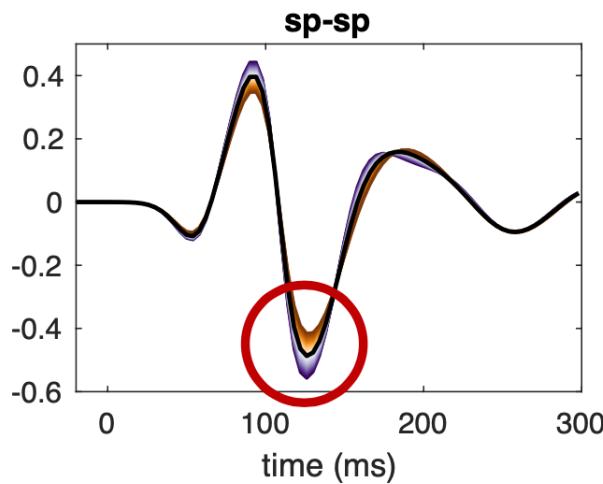
Scz > Rel, 40 Hz ASSR



Scz > Con, rsfMRI

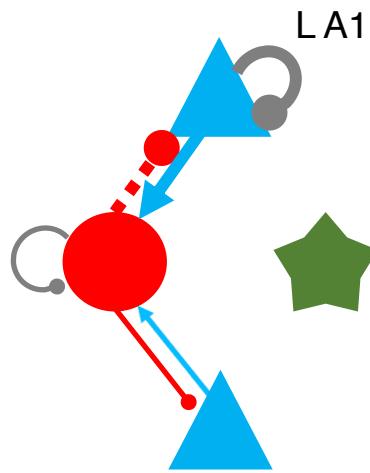
Cross-paradigm findings

Simulations confirmed sup pyramidal gain reproduces MMN and ASSR changes
...but interneuron gain does not

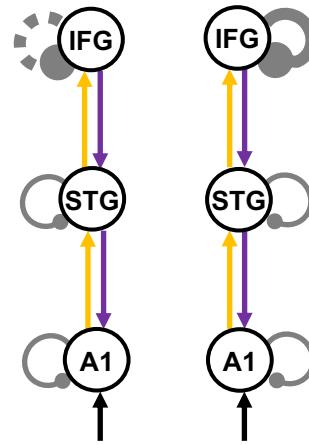


Cross-paradigm findings

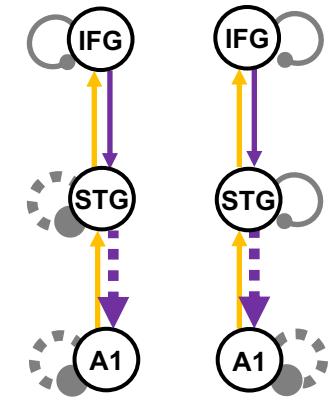
Summary: there are some striking consistencies across paradigms –
Abnormal auditory perceptions linked to disinhibition in auditory areas
...are symptoms the price the brain pays for restoring network excitability?



Scz & APTS Trait, ASSR (40 Hz)



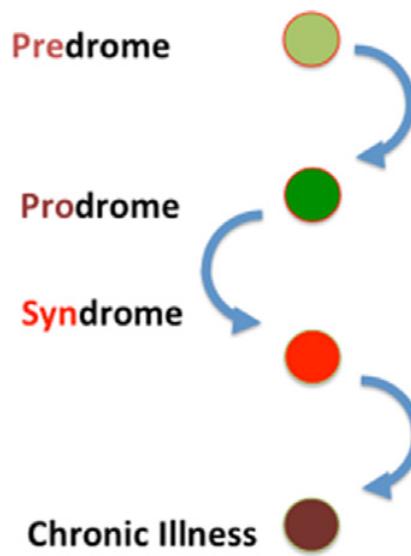
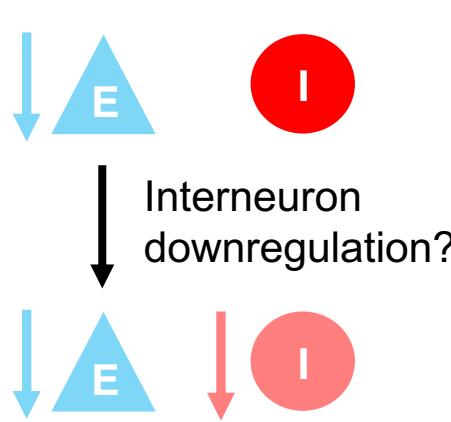
Scz & APTS State, MMN



Scz & APTS State, rsfMRI

Cross-paradigm findings

Summary: there are some striking consistencies across paradigms –
Abnormal auditory perceptions linked to disinhibition in auditory areas
...are symptoms the price the brain pays for restoring network excitability?

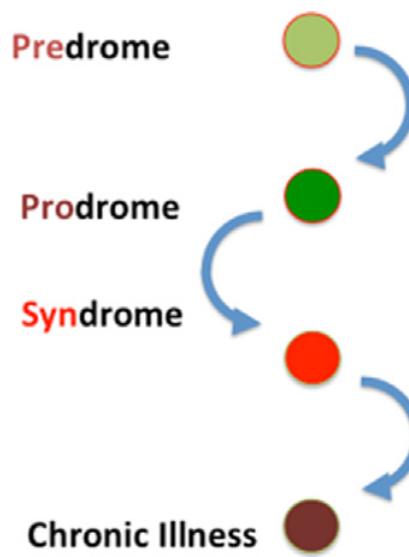
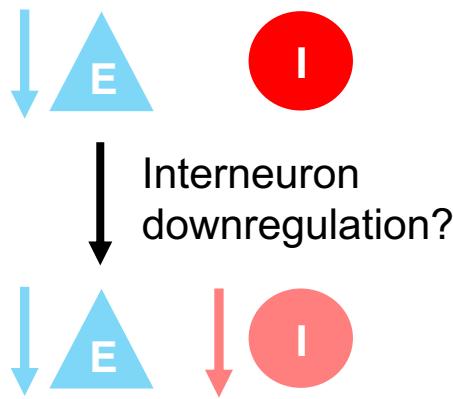


State of the Network

- **Deficit:** Glutamate Synaptic Dysfunction
- **Consequence:** Glutamate signaling deficit
- **Allostatic Adaptation:** GABA deficit and programmed synaptic proliferation
- **Consequence:**
 - E/I Imbalance (Disinhibition)
 - Tuning Deficit, Oscillation Abnormalities
 - Hyperconnectivity
- **Allostatic Adaptation:** Synaptic downscaling and programmed synaptic elimination
- **Consequence:**
 - Atrophy compounds synaptic deficit
 - Tuning deficits persist
 - Network functions decline

Inferring NMDA receptor function

Can we infer NMDA receptor function more directly?

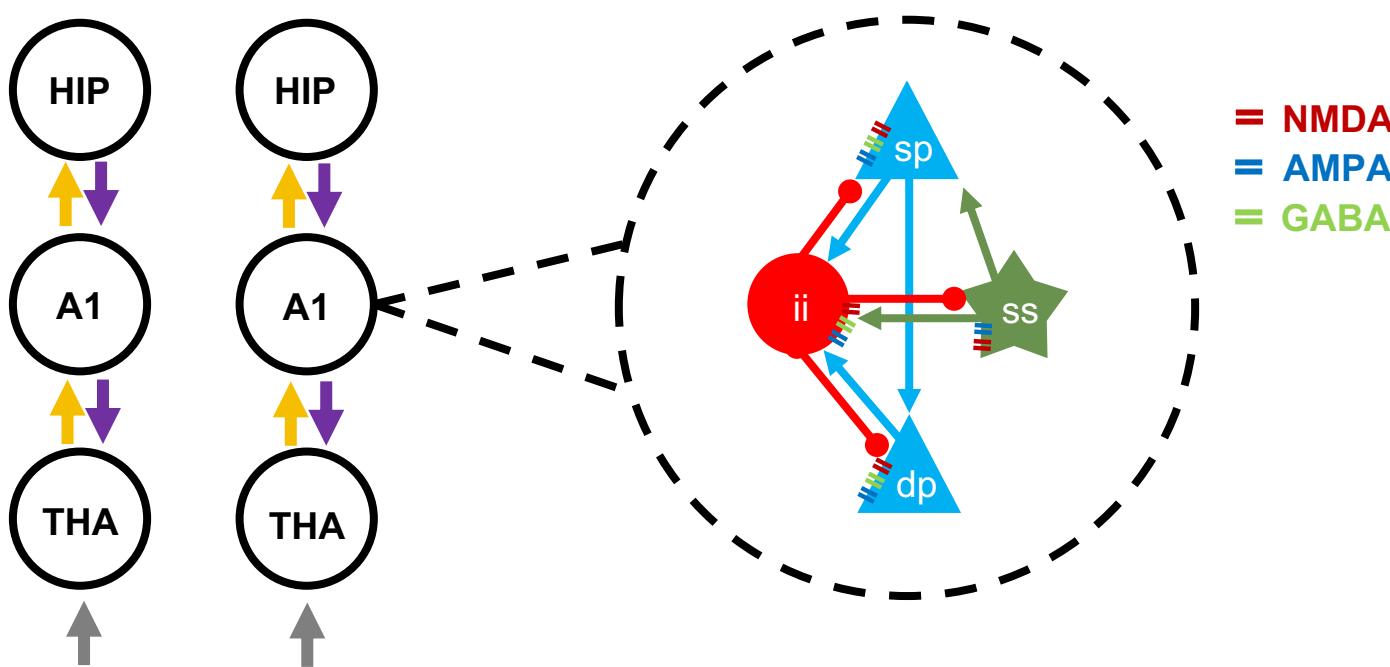


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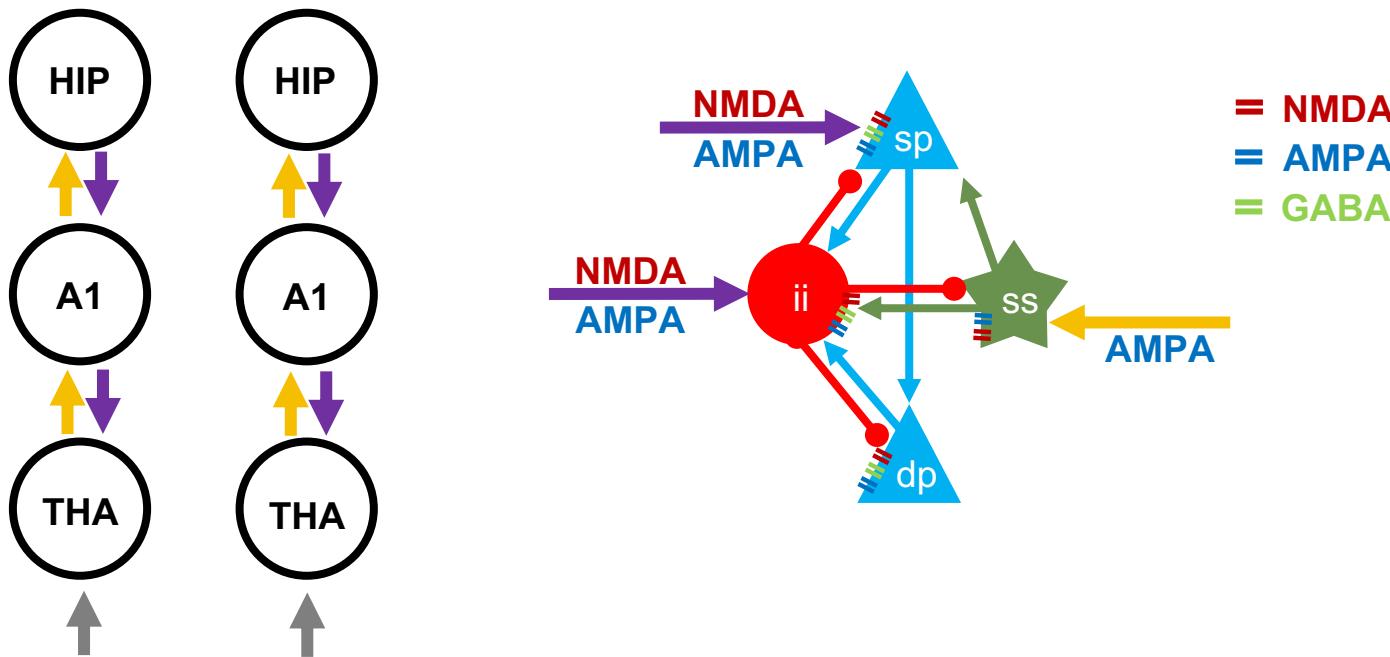
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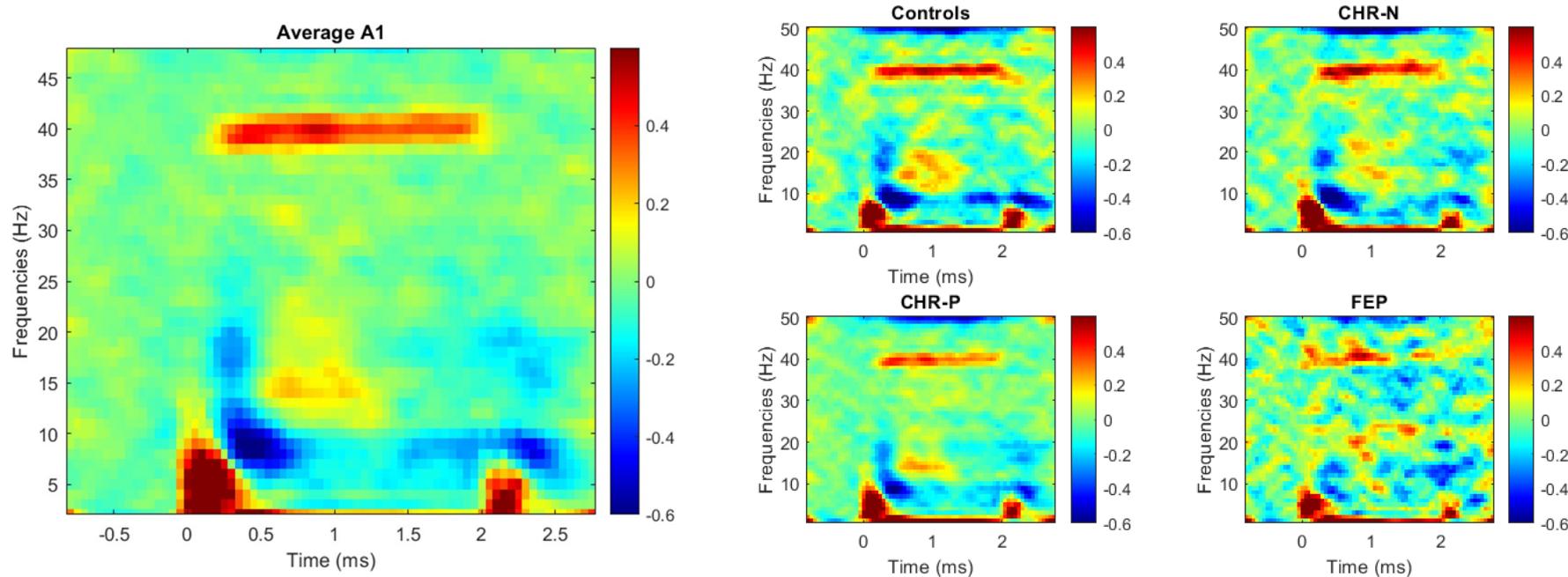
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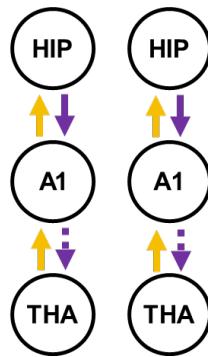
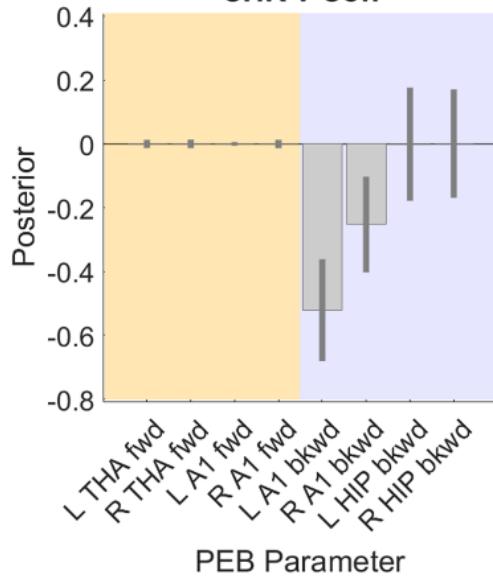
40Hz auditory steady state power is reduced in ‘high-risk’ people (who later develop psychosis: CHR-P) & first episode psychosis (FEP)



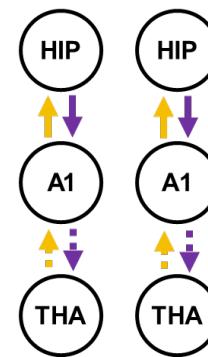
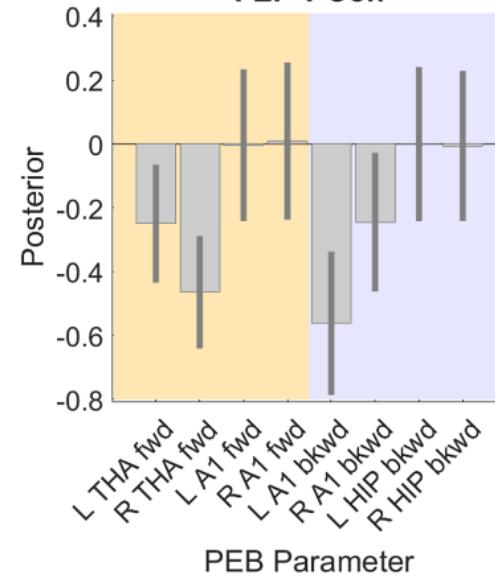
Inferring NMDA receptor function

Both high risk (CHR) and first episode (FEP) groups show loss of NMDA receptor-mediated connections from auditory cortex to thalamus

Extrinsic connectivity parameters:
CHR v Con

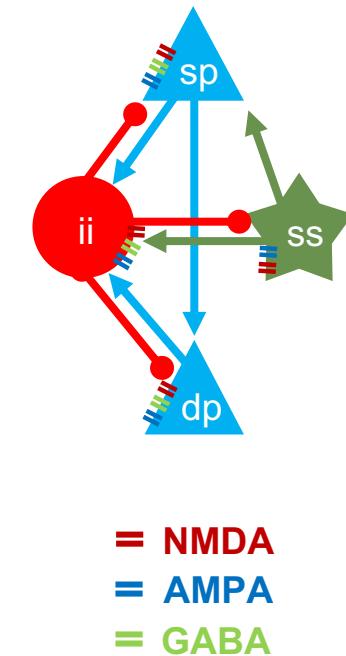
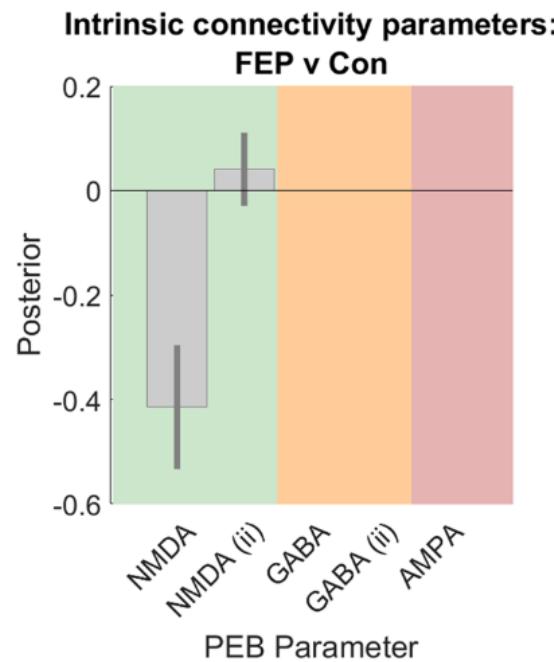
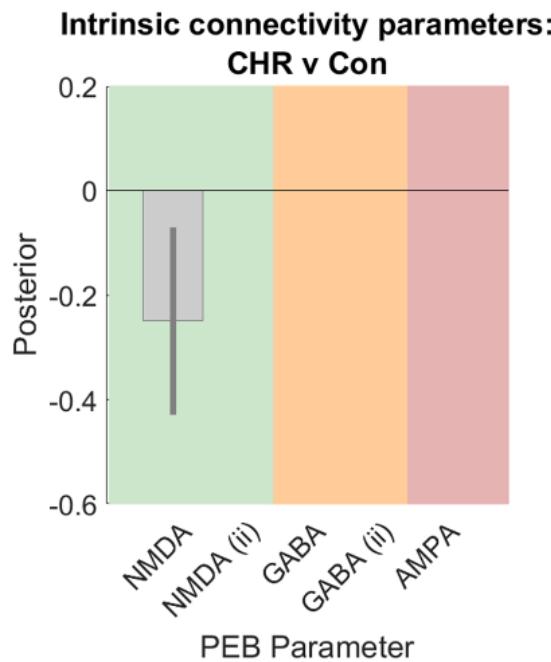


Extrinsic connectivity parameters:
FEP v Con



Inferring NMDA receptor function

Both high risk (CHR) and first episode (FEP) groups also show loss of microcircuit NMDA receptor function (on pyramidal cells)



Chronic psychosis



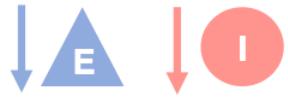
Network damage,
loss of connections

\downarrow E & \downarrow I cell function in psychosis

Early psychosis



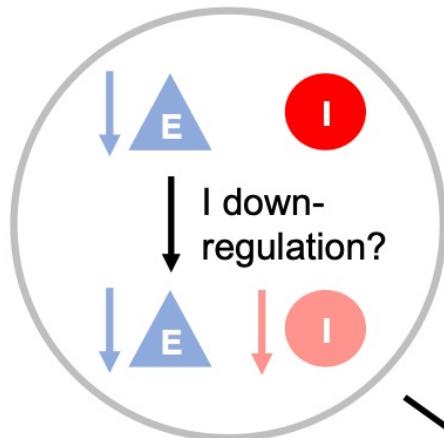
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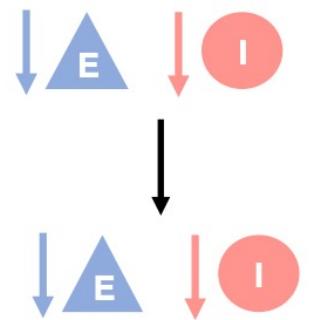
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two stages?

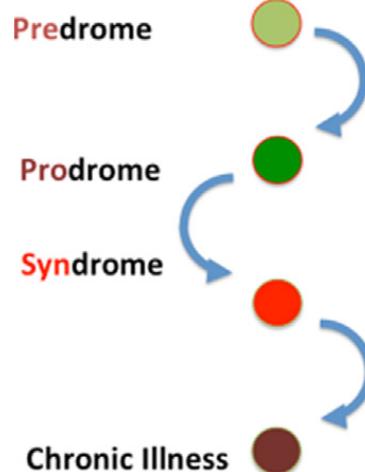


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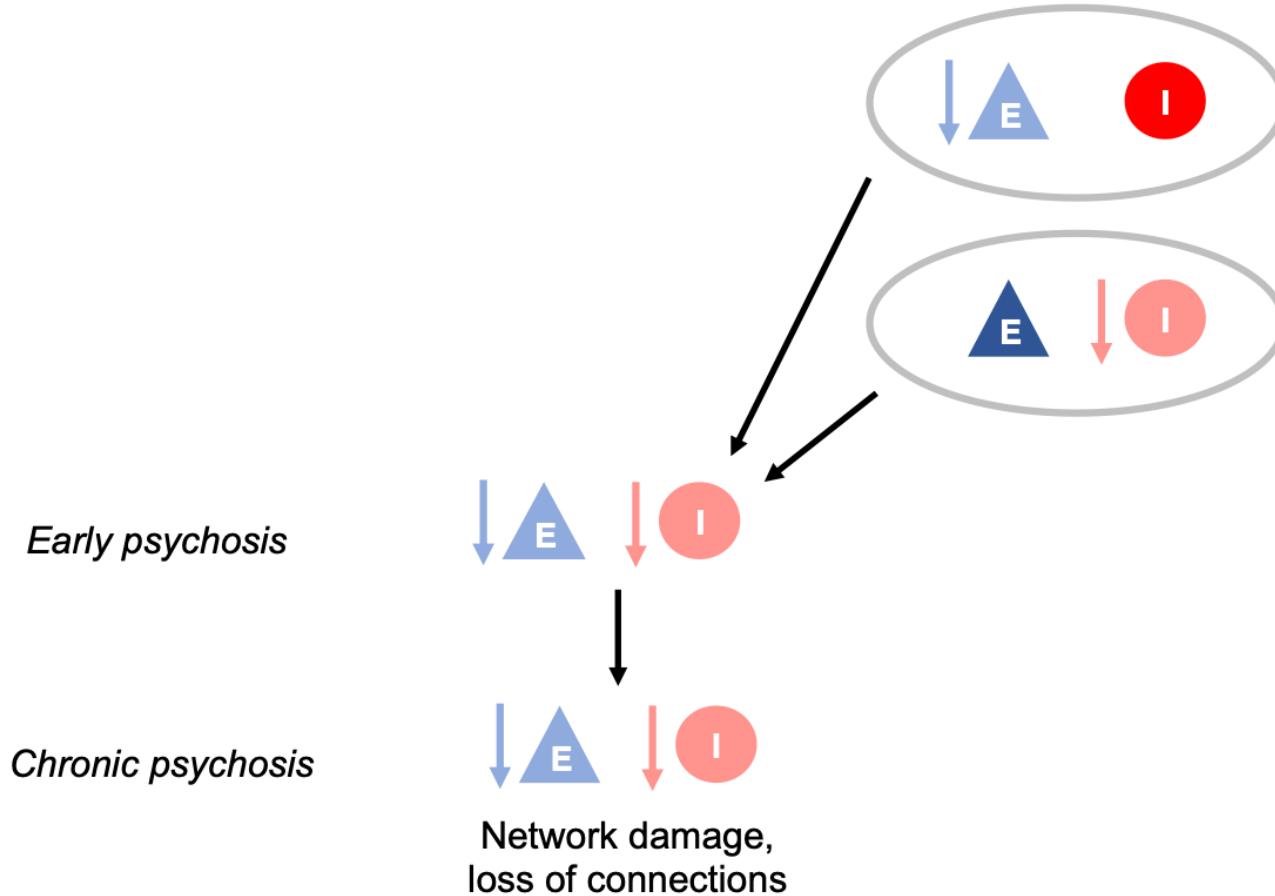
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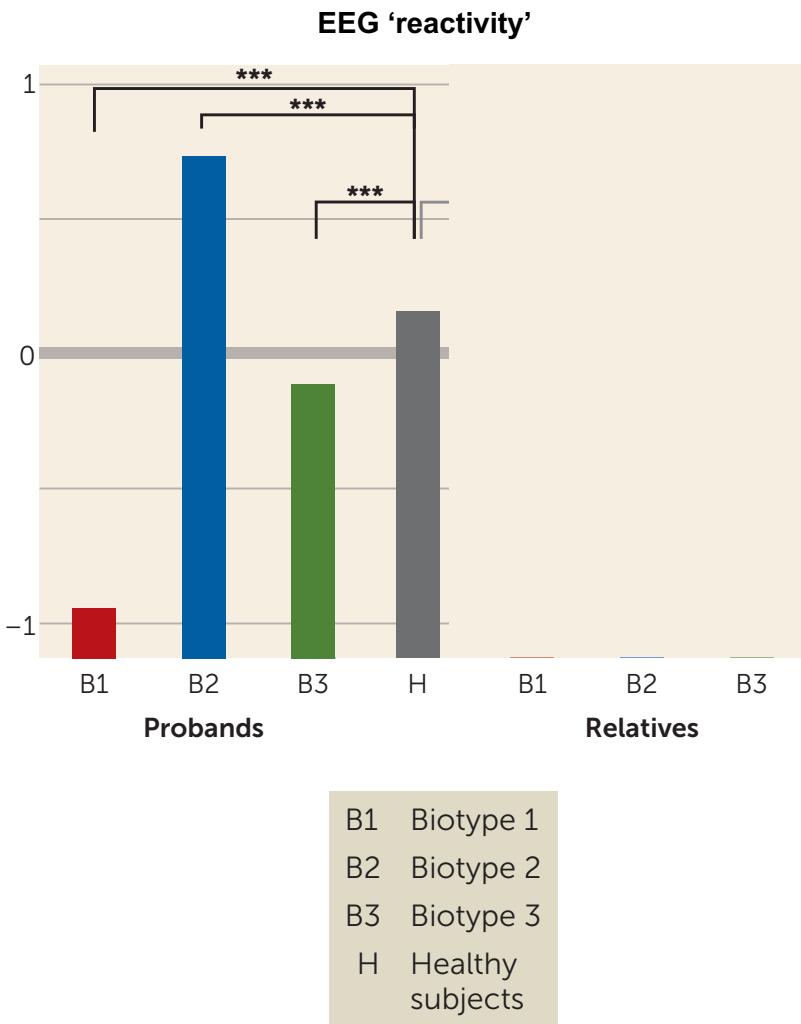
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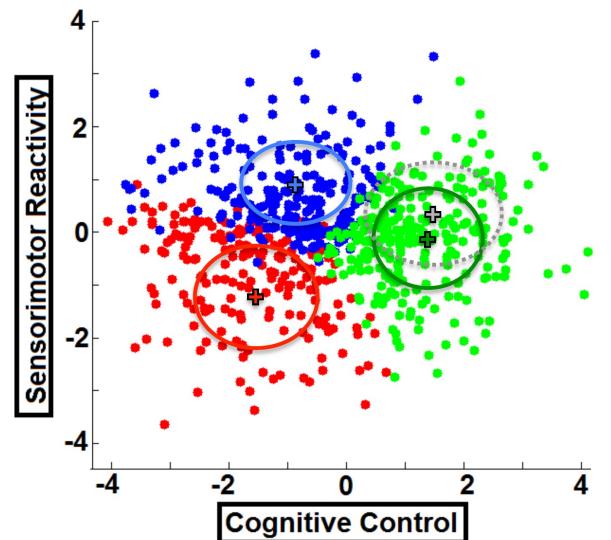
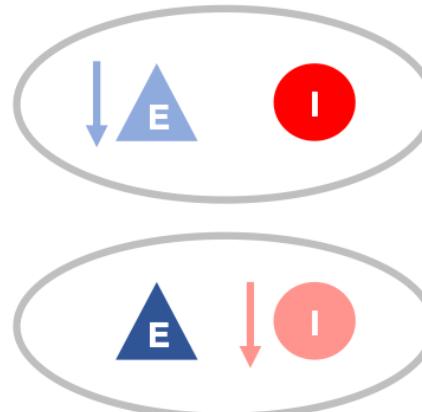
two syndromes?



Subgroups within psychosis

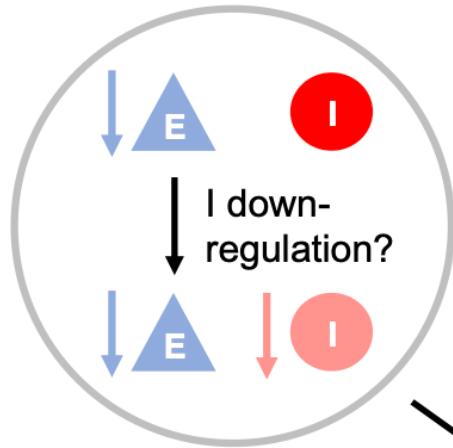


two syndromes?



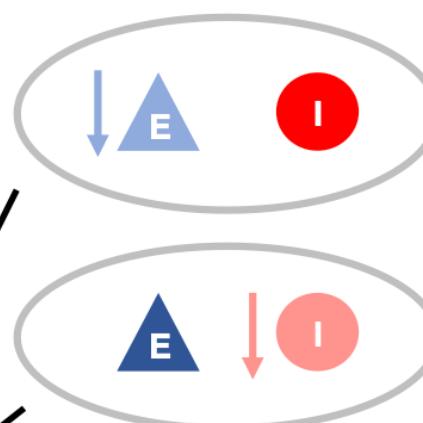
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two stages?



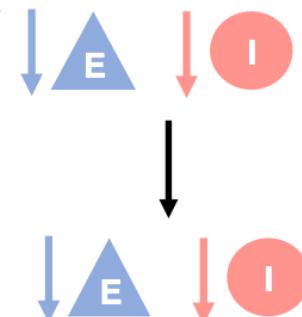
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Early psychosis

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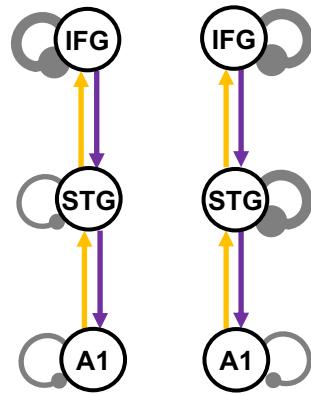
Network damage,
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These scenarios have
very different
treatment
implications...

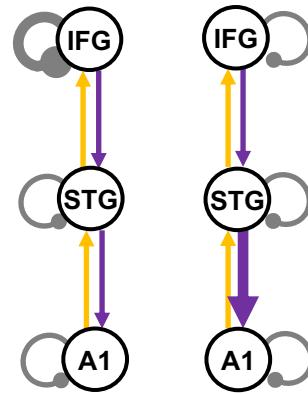
Subgroups within psychosis

rsfMRI MMN network 'biotypes' analysis (n=521)

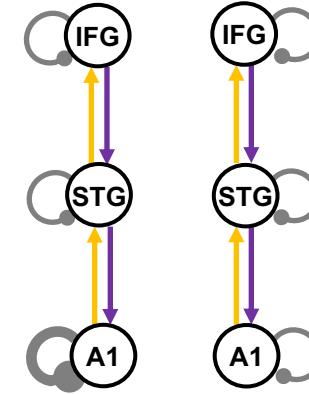
Loss of excitability again ~relates to psychosis subtypes



Biotype 1
(>Scz)



Biotype 2



Biotype 3

Results surviving correction for age, sex, site and CPZ

Conclusions

Initial modelling evidence =>

Group effect in Scz (both early and chronically unwell) is loss of excitability of pyramidal cells, probably due to NMDA receptor hypofunction

Psychotic symptoms (like hallucinations) may be the result of homeostatic disinhibition

Some evidence that 'biotypes' differ according to E and I microcircuit properties...

Key remaining questions...

Do subgroups show consistent results across paradigms? How best to identify them?

Can we give different glutamatergic treatments to different groups?