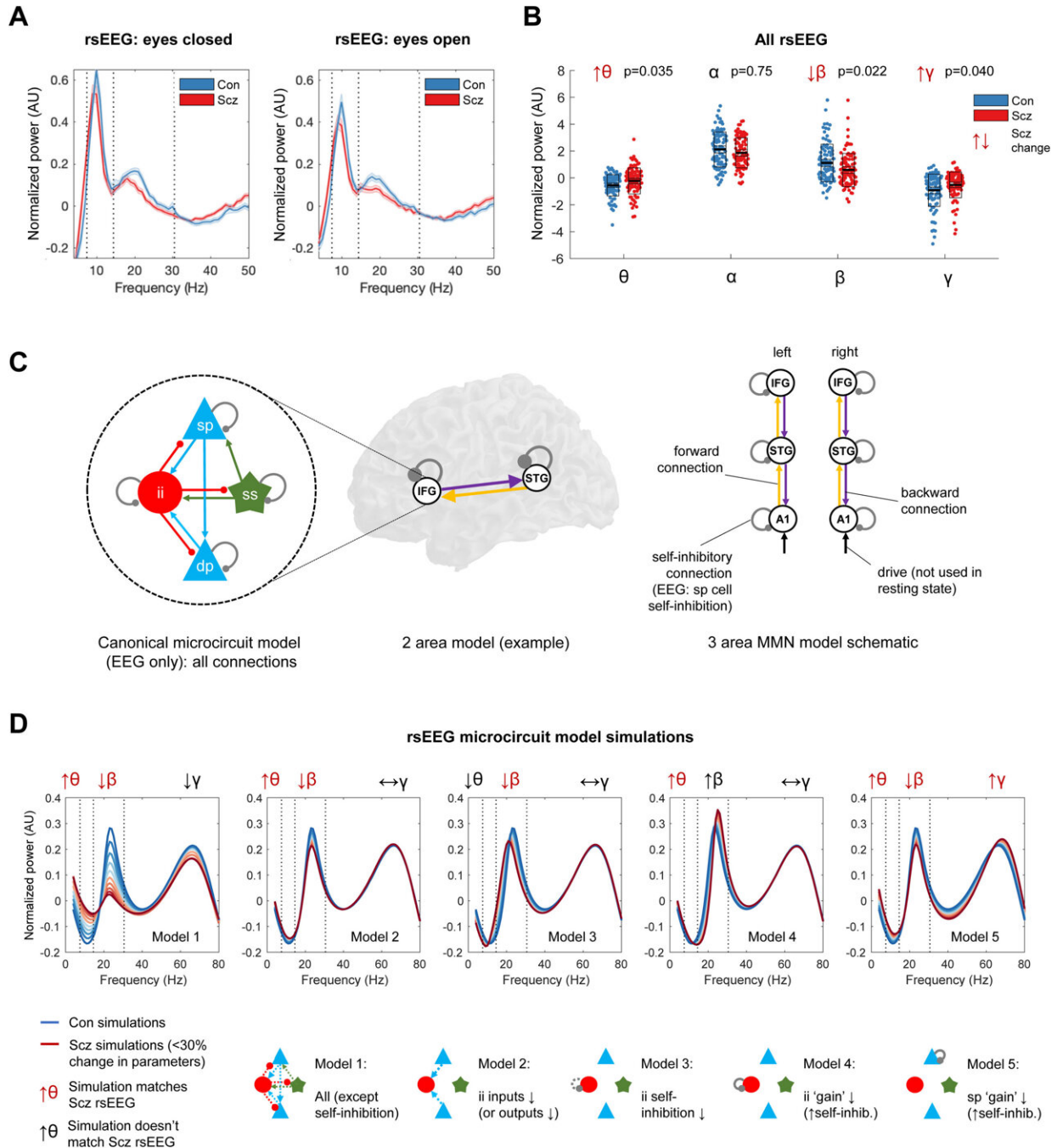


# Synaptic dysfunction in schizophrenia

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rsEEG results, DCM model structure and rsEEG simulations. A – The mean normalized eyes closed and eyes open rsEEG power spectra ( $\pm$ s.e.m.) across all channels for Con (n=98; blue) and PScz (n=95; red) groups, divided into four frequency bands (dotted lines):  $\theta$  (3-7 Hz),  $\alpha$  (8-14 Hz),  $\beta$  (15-30 Hz) and  $\gamma$  (>31 Hz). B – Group comparisons in mean power across both eyes closed and eyes open conditions in the  $\theta$ ,  $\alpha$ ,  $\beta$  and  $\gamma$  bands are shown. The box plots show the mean, s.e.m. and std. P values are Bonferroni-corrected for four comparisons. C – The EEG DCMs used the current version of the canonical microcircuit model (59) (also see Figure S1A). This microcircuit (shown left) consists of superficial and deep pyramidal cells (sp and dp), inhibitory interneurons (ii), and spiny stellate (ss) cells. They are interconnected with excitatory (arrowheads) and inhibitory (beads) connections; their self-inhibitory connections parameterize their responsiveness to their inputs, i.e. synaptic gain. In EEG DCM, each modeled cortical area contains a microcircuit (middle); fMRI DCM uses a much simpler neuronal model. Both DCMs have self-inhibition parameters (round gray beads) which, in the EEG case, inhibit superficial pyramidal cells specifically. A schematic DCM diagram is explained on the right. D – The top row shows the results of five sets (Models 1–5) of simulations of microcircuit parameter changes and their similarity to the rsEEG changes in  $\theta$ ,  $\beta$  and  $\gamma$  bands in PScz (the model does not produce an  $\alpha$  peak). The parameters changed in each model are illustrated in the microcircuit schematics for Models 1-5 (bottom row): parameter increases are denoted by whole lines and decreases by dotted lines. Each model is used to produce 10 simulations, starting with standard parameter values (to simulate Con) plotted in dark blue, and then reducing or increasing the parameters illustrated below in increments of 3% to simulate PScz (up to the most extreme change, plotted in dark red). Only Model 5, an increase in superficial pyramidal self-inhibition, i.e. a loss of synaptic gain, reproduces the changes seen in all three frequency bands. Credit: DOI: 10.1016/j.biopsycho.2021.07.024

**Schizophrenia, which can cause disrupted thought and mood, delusions and hallucinations, is among the most debilitating mental disorders and the most mysterious.**

Researchers have long suspected that the symptomology of [schizophrenia](#) fundamentally arises from disrupted synaptic function, or abnormalities in the way that neurons communicate with one another, perhaps leading to an imbalance between excitatory and inhibitory transmission.

Now, a new study has shown that schizophrenia itself is associated with a loss of excitation, but [hallucinations](#) and other symptoms are associated with a loss of inhibition. The study appears in *Biological Psychiatry*, published by Elsevier.

The authors, led by Rick Adams, Ph.D., at University College London, used electroencephalography (EEG), a noninvasive technique that measures [brain waves](#), to collect data from 107 participants with a diagnosis of schizophrenia, 57 of their relatives and 108 control participants. The EEGs of people with schizophrenia displayed hallmark signs including increased theta waves.

"The nature of [brain](#) circuit changes in schizophrenia is unclear," said Dr. Adams. "Is it too much excitation or not enough, or too much inhibition or not enough, or some combination?"

To find out, Dr. Adams and colleagues used computational modeling of the EEG data, which showed that the EEG differences seen in people diagnosed with schizophrenia resulted from decreased synaptic gain. This means that excitatory neurons had a diminished ability to stimulate one another. Symptoms of schizophrenia including [auditory hallucinations](#), however, were associated with a loss of neural inhibition, especially in auditory brain areas.

"This might mean that the loss of excitation comes first, and the brain tries to compensate for this by reducing [inhibition](#), but then this leads to hallucinations," Dr. Adams said. "Imagine you are trying to listen to

someone speaking on the radio, but the signal is very weak; if you turn the volume up, the speech is louder—but so is all the static and background noise—and so you may mistake some of this noise for actual speech. Something analogous might be happening in brain circuits in schizophrenia."

John Krystal, MD, Editor of *Biological Psychiatry*, said of the work: "Working out the fundamental features of synaptic dysfunction in schizophrenia may help to guide both pharmacological and neurostimulation treatments for this disorder."

**More information:** Rick A. Adams et al, Computational modelling of EEG and fMRI paradigms indicates a consistent loss of pyramidal cell synaptic gain in schizophrenia, *Biological Psychiatry* (2021). [DOI: 10.1016/j.biopsych.2021.07.024](https://doi.org/10.1016/j.biopsych.2021.07.024)

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