Synaptic gain abnormalities in schizophrenia, and the potential relevance for cognition

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An influential biological framework for understanding the neurobiology of schizophrenia invokes an imbalance of excitation and inhibition within cortical circuits (E/I imbalance), and this notion is supported by electrophysiological, neuropathological and molecular imaging findings (1). An E/I imbalance might conceivably arise from a primary disruption in synaptic gain, where the latter refers to sensitivity of a post-synaptic neuron to change in a presynaptic input (i.e. the steepness of the slope of the input-response relationship, **Figure 1A**). Synaptic gain is a fundamental biophysical property of neuronal function, and gain modulation is considered necessary for multiple forms of neuronal computation. However, a direct measurement of synaptic gain requires invasive electrophysiology recordings, and this is not easily possible in clinical samples. As a consequence, the question of an abnormality in synaptic gain in schizophrenia remains unanswered, including whether a putative abnormality is (1) differentially expressed in distinct neuronal subpopulations (which has consequences for molecular treatment targets), and (2) is capable of explaining previously disparate electrophysiological markers of the condition.

In this present issue of *Biological Psychiatry*, Adams and colleagues (2) set out to answer these questions in a large sample of people with schizophrenia diagnoses (PScz, n = 108), their first degree relatives (n = 57), and control participants (n = 107), using electroencephalography (EEG) recordings and computational modelling. This rich dataset included EEG recordings during resting state (rsEEG), in addition to evoked-response (task) paradigms that previously revealed robust EEG differences between PScz and controls (i.e.

mismatch negativity (MMN) and 40 Hz auditory steady state response (ASSR)). Although differential EEG patterns between PScz and controls have previously been construed within a framework of E/I imbalance, it is unknown whether a single synaptic abnormality can account for EEG findings across both rest and task evoked conditions.

Traditional analytic methods for EEG are ill-equipped to answer questions pertaining to synapse-level abnormalities. To overcome this limitation, Adams and colleagues leverage a computational modelling framework – Dynamic Causal Modelling (DCM) – that formally specifies how population-level potentials (as detected by EEG) are generated by the underlying activation dynamics of neurons within the cortex (a specification referred to as a 'generative model'). The generative model used takes the form of a canonical cortical microcircuit, which specifies the synaptic relationships between 4 neuronal subpopulations within a single cortical area (excitatory superficial and deep pyramidal cells ('sp' and 'dp') and spiny stellate ('ss') cells, and inhibitory interneurons ('ii')) in the form of coupled differential equations (**Figure 1B**). These equations (i.e. the structural form of the model) capture the *kinds* of interactions between subpopulations that are permitted within a cortical area (e.g. connection between 'sp' and 'ii'). The precise *strength* of these interactions is then governed by the model parameterisation, where parameters have plausible biophysical interpretations (e.g. connection *strength* between 'sp' and ii' populations). These free parameters allow DCM models to be fitted to EEG data using Bayesian methods, which infer the most likely parameter values for each participant (or group) given both the observed data, and prior information from previous neurophysiological studies. In principle, this approach allows researchers to ask not only which microcircuit parameters contribute to observed group differences in EEG features, but also to test whether these same parameter differences account for qualitatively different EEG measures across paradigms (which can be modelled using the same DCM microcircuit model, nested within task-specific macroscopic models of inter-region interactions, **Figure 1B**).

Strikingly, Adams and colleagues find that a single parameter difference in PScz – increased (superficial) pyramidal cell 'self-inhibition' – could account for observed EEG differences between PScz and controls across all paradigms (rsEEG, MMN and 40 Hz AASR). Pyramidal cell 'self-inhibition' governs the slope of an input-output function of these neurons. Adams and colleagues thus interpret 'increased self-inhibition' as 'reduced synaptic gain' on pyramidal neurons, after considering multi-synaptic 'self-inhibition' mechanisms (e.g. an increased influence of a 'sp-ii-sp' circuit) as a less plausible interpretation given prior neuropathological findings. This new finding is in line with an hypothesis that a primary synaptic pathology in schizophrenia impacts upon (excitatory) pyramidal neurons. Of note, an

analogous ‘self-inhibition’ increase on interneurons is unable to account for EEG differences between PScz and controls, leading to a hypothesis that previously detected reductions in cortical interneurons in PScz, reported in post-mortem studies, may be a consequence of secondary interneuron downregulation. Such downregulation would be expected to occur in the presence of reduced excitatory function, as neuronal circuits use multiple ‘homeostatic’ mechanisms to maintain a certain level of activation (3).

An important question, with critical importance for therapeutic translation, relates to the receptor-level mechanisms that drive a reduction in the inferred synaptic gain reduction. Here, Adams and colleagues suggest a reduction in N-methyl-D-aspartate receptor (NMDAR) signalling as the most likely candidate, informed by multiple independent lines of evidence that implicate cortical NMDAR hypofunction in schizophrenia. If this is indeed the case it is intriguing to speculate about the functional consequences of such a receptor-level abnormality. Cortical NMDAR function is arguably best understood in the context of NMDAR-dependent synaptic plasticity within hippocampal-entorhinal cortex (HEC). Although HEC has long been considered integral for spatial navigation and long-term memory, it is now understood to support a broader mode of cognition pertaining to the relationships (associations) between entities across a wide variety of domains (4). This is a mode of cognition we have suggested is important for understanding the myriad symptomatic manifestations of schizophrenia, from abnormal inferences in paranoia to a loosening of semantic associations in thought disorder (5).

A particularly striking example of such structured neuronal representation in HEC (i.e. representation of the relationships between entities or task states) is the phenomenon of neural replay. Here hippocampal state reactivations (e.g. place cell reactivations) spontaneously recapitulate learned sequential associations between states (e.g. trajectories through space) while an animal is at rest (6). Replay is implicated in memory consolidation, credit assignment and inference. Intriguingly, replay is disrupted in a genetic mouse model of schizophrenia (7), a finding we recently corroborated in a sample of PScz, using a neural decoding method applied to resting state magnetoencephalography (MEG) data (5).

The findings of Adams and colleagues are directly relevant here. First, microcircuit E/I dysfunction in PScz (e.g. loss of excitatory gain and interneuron downregulation) is likely to have profound consequences for the temporal coordination of hippocampal reactivations, which are exquisitely sensitive to perturbations in interneuron function (8). Second, if E/I imbalance is secondary to pyramidal neuron NMDAR hypofunction, then we should expect to observe consequences for replay stemming from a disruption in NMDAR-dependent plasticity.

NMDAR-dependent plasticity is necessary for encoding new associative representations within hippocampus, and is thus a pre-requisite for the subsequent spontaneous reactivation of such representations in the context of replay (9,10).

We believe we are now entering an exciting time in the evolution of biological and computational psychiatry, where theoretical and methodological chasms between disparate domains of enquiry are closing. Adams and colleagues provide a paradigmatic example of one such case, in which advances in computational analysis permit microcircuit-level inferences to be made from non-invasive brain recordings. These findings explain previous EEG abnormalities within a unifying circuit-level framework, and thus represent a significant advance in our knowledge of schizophrenia. An important interpretational caveat, acknowledged by the authors, is that receptor-level inferences cannot be fully addressed by the DCM microcircuit model used in the present study, which lacks an explicit parameterisation of NMDAR currents. Consequently, we look forward to future studies that seek to validate DCM model predictions in paradigms with a known molecular or circuit-level 'ground truth' (e.g. using pharmacological and optogenetic manipulations, respectively). Furthermore, we consider it will be equally important to rigorously investigate cognitive consequences of putative circuit-level abnormalities, where disrupted neural replay represents one example.

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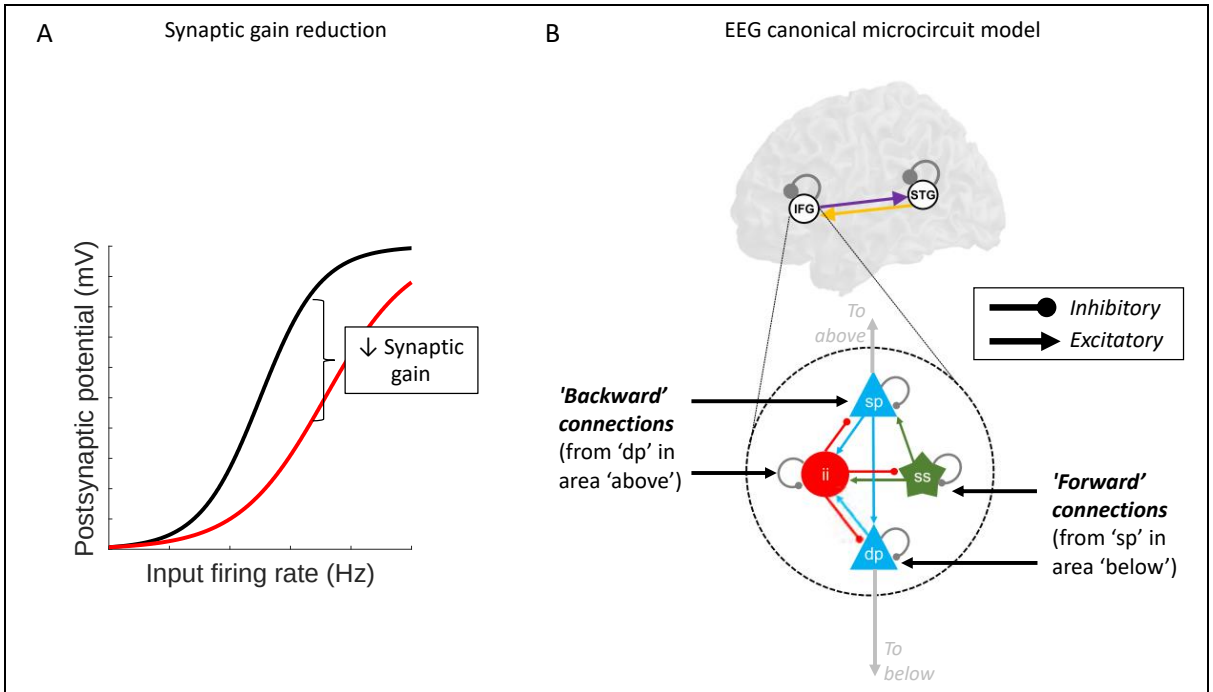

Figure 1. Dynamic causal modelling to infer alterations in synaptic gain.
(A) Synaptic gain describes the sensitivity of a (postsynaptic) neuron's membrane potential to variations in the strength of its (presynaptic) inputs. A reduction in synaptic gain corresponds to a divisive (as opposed to subtractive) decrease in this sensitivity (i.e. a reduction in the slope of the input-response relationship).
(B) Illustration of canonical cortical microcircuit model used for DCM. This model contains 4 neuronal populations (superficial and deep excitatory pyramidal cells [sp & dp], excitatory spiny stellate cells [ss], and inhibitory interneurons [ii]) and the connection strengths between them (arrows). 'Self-inhibition' corresponds to the inhibitory arrows from a neuronal population to itself. Of note, for task EEG only a subset of the connection strengths were treated as free parameters during model fitting (notably, self-inhibition on 'sp' and 'ii', and connections between 'ii' and both 'sp' and 'dp'). For task EEG, microcircuit models were nested within a macroscopic model structure describing the interaction between different brain areas (example shown for a '2 area' macrocircuit). Figure adapted from Adams et al,. (2021), with permission.

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