



Neuropharmacological computational analysis of longitudinal electroencephalograms in clozapine-treated patients with schizophrenia using hierarchical dynamic causal modeling

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ABSTRACT

The hierarchical characteristics of the brain are prominent in the pharmacological treatment of psychiatric diseases, primarily targeting cellular receptors that extend upward to intrinsic connectivity within a region, interregional connectivity, and, consequently, clinical observations such as an electroencephalogram (EEG). To understand the long-term effects of neuropharmacological intervention on neurobiological properties at different hierarchical levels, we explored long-term changes in neurobiological parameters of an N-methyl-D-aspartate canonical microcircuit model (CMM-NMDA) in the default mode network (DMN) and auditory hallucination network (AHN) using dynamic causal modeling of longitudinal EEG in clozapine-treated patients with schizophrenia. The neurobiological properties of the CMM-NMDA model associated with symptom improvement in schizophrenia were found across hierarchical levels, from a reduced membrane capacity of the deep pyramidal cell and intrinsic connectivity with the inhibitory population in DMN and intrinsic and extrinsic connectivity in AHN. The medication duration mainly affects the intrinsic connectivity and NMDA time constant in DMN. Virtual perturbation analysis specified the contribution of each parameter to the cross-spectral density (CSD) of the EEG, particularly intrinsic connectivity and membrane capacitances for CSD frequency shifts and progression. It further reveals that excitatory and inhibitory connectivity complements frequency-specific CSD changes, notably the alpha frequency band in DMN. Positive and negative synergistic interactions exist between neurobiological properties primarily within the same region in patients treated with clozapine. The current study shows how computational neuropharmacology helps explore the multiscale link between neurobiological properties and clinical observations and understand the long-term mechanism of neuropharmacological intervention reflected in clinical EEG.

1. Introduction

The human brain is a complex hierarchical system composed of interactions at different levels, from microscale neurons to macroscale brain networks. This hierarchical characteristic is prominent in the treatment of psychiatric diseases. As a most common treatment, antipsychotic medication, which primarily targets cellular-level neuroreceptors, is expected to induce long-term changes in the intraregional connectivity and interregional brain circuitry and, consequently, routine clinical elec-

trophysiology. Thus, understanding the hierarchical effects of antipsychotic medications on clinical electrophysiology, particularly an electroencephalogram (EEG), is critical to dissect the long-term mechanism of neuropharmacological intervention and to adjust treatment methods.

Despite the widespread use of drugs and many reports on drug-induced EEG changes (Adams et al., 2022; Hyun et al., 2011; Jackson and Seneviratne, 2019; Knott et al., 2001; Ozaki et al., 2021; Raymond et al., 2022), there is scant information on the long-term neuropharmacological alterations at the cellular properties, intrinsic connectiv-

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ity among excitatory and inhibitory neural populations, and extrinsic interregional connectivity, induced by antipsychotic medications. The effects of those neural properties on EEG alterations are also poorly understood. The resolution of neuropharmacological effects on multiscale neural properties is very challenging, as we need more knowledge of the complex hierarchical mechanisms of neuropharmacology. It is also nontrivial to observe activities at all hierarchical levels for exploration. However, computational modeling with biologically plausible assumptions may help to address these challenges.

In the present study, using dynamic causal modeling (DCM) (Friston et al., 2003) of longitudinal EEG, we investigated long-term changes in neural properties at different hierarchical levels in patients with schizophrenia treated with clozapine and proposed methods to specify the effects of neural properties and their nonlinear interactions on cross-spectral density (CSD) of EEG.

Schizophrenia, a major mental spectrum disorder of unknown etiology (McCutcheon et al., 2019), has positive symptoms (delusions, hallucinations, and disorganized behavior), negative symptoms (diminished emotional expression or motivation) and cognitive dysfunction (deficiencies in attention, working memory, and executive functioning). Antipsychotic medications, such as risperidone, olanzapine, paliperidone, quetiapine, aripiprazole, haloperidol, and chlorpromazine, are the most recommended treatments for schizophrenia. Among various antipsychotic drugs, clozapine has been used for treatment-resistant patients with schizophrenia who do not respond to typical and atypical antipsychotics (McEvoy et al., 2006).

Clozapine, a mild agonist of N-methyl-D-aspartate (NMDA) receptors, acts on several neurotransmitter receptors (O'Leary and Nolan, 2015). Despite its efficacy, the mechanisms of clozapine are not fully understood. Particularly, there is a dearth of information on how it changes brain circuits longitudinally and how it alters schizophrenia EEGs over long periods (Ravan et al., 2015; Risby et al., 1995).

To address these questions, we chose patients with refractory schizophrenia who were treated with clozapine. Clozapine remains the only drug licensed to treat refractory schizophrenia (Flanagan et al., 2020), and the dosage of clozapine for the control of symptoms in refractory period has not changed much for a long time. The relatively constant drug dose in clozapine-medicated patients is advantageous for exploring clozapine treatment mechanisms that induce long-term electrophysiological changes. This is important as the effect of the psychotropic drug on EEG due to the change in dosage could be minimized.

We adopted DCM with a canonical microcircuitry model (CMM) with NMDA, called the CMM-NMDA model (Adams et al., 2020; Pereira et al., 2021; Symmonds et al., 2018). As a conductance-based neural state model (Moran et al., 2013a; 2011; Pereira et al., 2021), the CMM-NMDA model formulates conductance changes of channel proteins such as the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and NMDA, within the neural context of intrinsic and extrinsic connectivity. For a review on the CMM-NMDA, see Pereira et al. (2021). The CMM-NMDA model can be considered a hierarchical model because it includes cellular-level neural properties for a subpopulation, intrinsic connectivity among subpopulations in a cortical column, and interregional extrinsic connectivity between cortical columns. Consequently, the CMM-NMDA model allows the exploration of changes in these neural properties throughout the hierarchy due to long-term medication.

For group analysis of longitudinal changes in neural properties with interindividual variability in medication duration (MDur, the duration between follow-up and baseline) and symptom improvement ratio (SI), we utilized the parametrical empirical Bayes (PEB) of DCM (Friston et al., 2015; 2016) with a group-level design matrix composed of those factors.

To apply the CMM-NMDA model to schizophrenia, we focused on the default mode network (DMN) and the auditory hallucination network (AHN). In schizophrenia, DMN is a common target of schizophrenia research with respect to autobiographical and attention-related symptoms

(Galindo et al., 2018; Garrity et al., 2007; Li et al., 2017; Sambataro et al., 2010; Swanson et al., 2011). AHN is not only related to auditory hallucinations, a major symptom of schizophrenia (Andreasen and Flaum, 1991; Stephane et al., 2001), but it is also the region commonly affected in schizophrenia. This is evident from the alteration of cortical thickness and metabolism in this region (Cui et al., 2018; Park et al., 2006).

We examined the effects of patient-specific MDur and SI on neural properties at each hierarchical level by taking advantage of the hierarchical structure of the CMM-NMDA. We further discerned how changes in specific neural properties in the CMM-NMDA model induce EEG CSD shifts at four different frequency bands (delta, theta, alpha and beta) by introducing a virtual perturbation analysis. We also proposed a method to explore nonlinear interaction effects between neural properties in altering EEG CSD.

We found that longitudinal neuropharmacological changes in clozapine-treated patients occurred widely at hierarchical levels. These included cellular-level properties, such as membrane capacitance and NMDA time constants, and intrinsic and extrinsic connectivity. Within the hierarchy, changes in intrinsic connectivity were dominant in explaining individual variations in MDur and SI. This was particularly evident in inhibitory interneurons.

Virtual perturbation analysis showed the role of each neural property in generating frequency shifts and the complementary excitatory-inhibitory role in explaining longitudinal changes in EEG CSD in clozapine-treated patients. We also found nonlinear interactions between neural properties in inducing positive and negative synergistic effects on the progression of CSD.

In doing so, we argue the importance of computational modeling, called computational neuropharmacology, in exploring the long-term effects of clozapine by linking clinical observations with the neural properties of its underlying neural circuitry. Furthermore, computational neuropharmacology will also help to understand the causal effects of each neural property and the interactions between neural properties on the progression of EEG CSD.

The current study comprises five sections. First, we briefly introduce a CMM-NMDA model. Second, we present the EEG preprocessing and spectral DCM modeling of individual resting-state EEG after determining the basic topology of DMN and AHN using Bayesian model selection. Third, we evaluated long-term longitudinal changes in cellular properties and intrinsic and extrinsic connectivity by associating them with MDur and SI in patients with schizophrenia medicated with clozapine. Fourth, we present methods to assess the sensitivity of each neural property or set of neural parameters in altering EEG CSD. We also introduce methods for evaluating the complementary process of excitatory-inhibitory neurons and nonlinear interaction effects between neural properties on EEG CSD changes and progression by virtually perturbing these properties in the computational model. Finally, we discuss the analysis results with empirical data and virtual perturbation analysis to demonstrate the utility of current neuropharmacological modeling.

2. Experimental data

2.1. Patients

Longitudinal clinical EEG data from 23 patients with schizophrenia treated with clozapine (13 males, 10 females), obtained as a clinical procedure at Dongguk University International Hospital, were used in the current study (Fig. 1A). EEG data were acquired twice: at the beginning of the first acquisition of EEG with stable clozapine treatment as a baseline and at the second follow-up EEG acquisition; the baseline age was 40.3 ± 8.1 (mean $\pm$ std, from now on) and the duration between the two sets of EEG data was 1047.1 ± 502.7 days. The mean doses of clozapine (with std) at baseline and follow-up were 251.1 ± 59.6 mg and 240.2 ± 66.5 mg. There were no significant differences in the dose of clozapine between follow-up and baseline ($p = 0.08$). The Positive and

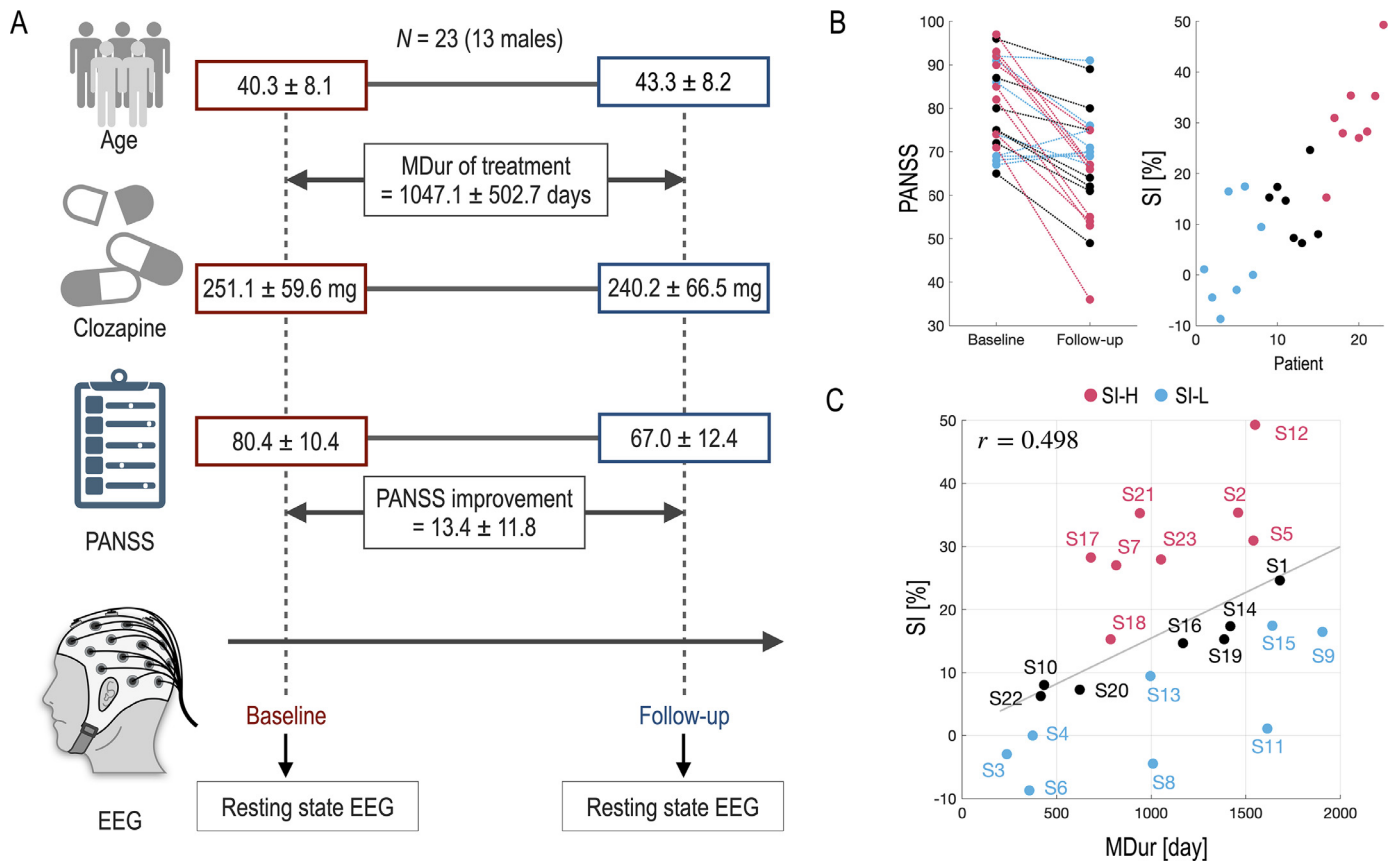


Fig. 1. Demographic information. (A) Longitudinal resting state EEG data were collected from 23 patients with schizophrenia at baseline and follow-up time points, with an average time (medication duration, MDur) between the two points of 1047.1 ± 502.7 days. The mean dose of clozapine at baseline was 251.1 ± 59.6 mg, and 240.2 ± 66.5 mg at follow-up. The average improvement in PANSS scores was 13.4 ± 11.8 . (B) PANSS score changes between baseline and follow-up and symptom improvement ratio (SI) are plotted. Patients with the highest 35% and lowest 35% SI were subdivided into the SI-H and SI-L groups. (C) Patients are displayed with respect to MDur and SI. The correlation between MDur and SI is $r = 0.498$.

Table 1
Demographic data of patients.

	All	SI-H (upper 35%)	SI-L (lower 35%)	two-sample <i>t</i> -test
Demographics				
Group size	23	8	8	
Gender	M 13:F 10	M 4:F 4	M 5:F 3	
Age [years]	$40.3 (\pm 8.1)$	$37.4 (\pm 4.1)$	$45.5 (\pm 10.8)$	$t = -2.00, p = 0.07$
duration [days]	$1047.1 (\pm 502.7)$	$1103.1 (\pm 360.5)$	$1016.6 (\pm 654.1)$	$t = 0.33, p = 0.75$
PANSS				
Baseline	$80.4 (\pm 10.4)$	$85.5 (\pm 9.3)$	$77.0 (\pm 10.8)$	$t = 1.68, p = 0.11$
Follow-up	$67.0 (\pm 12.4)$	$59.1 (\pm 12.2)$	$73.6 (\pm 7.6)$	$t = -2.85, p = 0.01^*$
Paired <i>t</i> -test	$t = 5.45, p = 0.000^*$	$t = 11.8, p = 0.000^*$	$t = 1.18, p = 0.28$	
Clozapine [mg]				
Baseline	$251.1 (\pm 59.6)$	$231.3 (\pm 83.2)$	$281.3 (\pm 45.8)$	$t = -1.49, p = 0.16$
Follow-up	$240.2 (\pm 66.5)$	$215.6 (\pm 81.2)$	$278.1 (\pm 41.1)$	$t = -1.94, p = 0.07$
Paired <i>t</i> -test	$t = 1.48, p = 0.15$	$t = 0.89, p = 0.41$	$t = 1, p = 0.35$	

* Indicates being statistically significant ($p < 0.05$) for paired *t*-test between follow-up and baseline, and two-sample *t*-test between SI-H and SI-L.

Negative Syndrome Scale (PANSS) scores at the follow-up were significantly reduced compared to baseline ($p < 0.001$). PANSS scores in the baseline phase do not correlate significantly with the dose of clozapine ($r = -0.382, p = 0.072$). Demographic information is summarized in Table 1.

We define the symptom improvement ratio (SI) according to the PANSS score as follows:

$$SI = (\text{PANSS}_{\text{baseline}} - \text{PANSS}_{\text{follow-up}}) / \text{PANSS}_{\text{baseline}}. \quad (1)$$

The mean and standard deviation of SI were 16.2 and 14.6. PANSS scores and SI are shown in Fig. 1B. SI is significantly correlated with medication duration (MDur) between the two acquisitions of EEG data ($r = 0.498, p = 0.016$) (Fig. 1C).

We divided all patients according to SI after regressing the MDur effect: patients with 35% upper (8 patients) and 35% lower as SI-H and SI-L groups (Fig. 1C). At baseline, the PANSS scores and the clozapine doses did not differ significantly between the SI-L and SI-H groups. However, PANSS scores were significantly lower in the SI-H group compared

to the SI-L group at follow-up ($p = 0.01$). Although all 23 patients' data were used for model selection, evaluation of frequency and edge-specific CSDs associated with SI and MDur, and evaluation of model parameters associated with SI and MDur, SI-H is the main target of evaluation, as it shows improvement in symptoms during the clozapine medication period, compared to the SI-L group that showed resistance to clozapine medication. We expected that focusing on the SI-H group would reduce inter-individual variations in exploring the relationship between neural properties and CSD changes. There were no significant differences between the SI-H and SI-L groups in CSD powers at each edge in each frequency band.

The institutional review board approved this retrospective study of Dongguk University International Hospital.

2.2. EEG acquisition and preprocessing

The EEGs with a frequency filter range of 0.1 and 100 Hz were recorded according to 10/20 systems with 32-channel EEG (Grass Technologies Comet-PLUS) at a sampling frequency of 400 Hz. Among the 32 channels, one channel was used for the electrocardiogram (ECG) and two for the electrooculogram (EOG). We resampled the data at 250 Hz, followed by high-pass filtering at 1 Hz and line noise removal using EEGLab, a MATLAB toolbox (<https://eeglab.org>). We utilized 'Clean rawdata EEGLAB plug-in' to remove bad and noisy channels with flat signals and low-frequency drifts. The channel signals removed were interpolated with spherical methods. All channels were re-referenced using common-average reference. We performed independent component analysis (ICA) using the Amica toolbox (https://scn.ucsd.edu/~jason/amica_web.html) to identify noisy components, which were classified using ICALabel. The signal was reconstructed by recombining all components with a residual variance (RV) of less than 0.15 and the probability of being the brain more than 70%. The continuous signals were epoched in 2 sec. To eliminate undesirable epochs, short-term Fourier transforms with a frequency range of 1–50 Hz were applied to epoched EEG signals. Epochs with a Z-score of more than three standard deviations were discarded. The analysis procedure is shown in Fig. 2.

2.3. Regions of interests for DMN and AHN

The brain regions of DMN and AHN were determined according to the previous literature (Jardri et al., 2011; Steen et al., 2019).

For DMN, the left lateral parietal lobe (ILP: Montreal Neurological Institute (MNI) coordinates -46, -66, 30), the right lateral parietal lobe (rLP: 49, -63, 33), the posterior cingulate / precuneus (PrCu: 0, -58, 0), and the medial prefrontal cortex (mPFC: -1, 54, 27) were chosen, according to the previous DCM EEG study (Steen et al., 2019).

For AHN, according to Jardri et al. (2011), we chose the left inferior frontal gyrus (lIFG: -50, 13, 5), the right inferior frontal gyrus (rIFG: 47, 10, -10), the left superior and middle temporal gyrus (STG: -56, -45, 14) and the left supramarginal gyrus (SMG: -55, -20, 14). Since EEG may not reliably capture deep brain activity, the hippocampus, and parahippocampal gyrus were excluded.

2.4. General linear model (GLM) analysis for normalized CSD differences

We analyzed longitudinal CSD changes in four frequency bands with respect to MDur and SI of patients. Four frequency bands are delta (1–3 Hz, δ), theta (4–7 Hz, θ), alpha (8–12 Hz, α), and beta (13–30 Hz, β). We normalized the original EEG CSD_{raw} by the Euclidean norm of CSD_{raw} across all frequencies (F , 1–40 Hz) and all edges (E) to reduce the effects of the EEG acquisition environment between sessions and between individuals.

$$CSD(e, f) = \frac{CSD_{\text{raw}}(e, f)}{\sqrt{\sum_{e \in E} \sum_{f \in F} CSD_{\text{raw}}(e, f)^2}}, \quad (2)$$

For DMN and AHN, the CSD matrix for each individual, $CSD(e, f)$, includes 10 edges (all unique edges among four regions under symmetric conditions) $\times$ 4 frequency bands. The CSD power difference between the follow-up and baseline is $\Delta_{CSD}(e, f) = CSD(e, f)_{\text{follow-up}} - CSD(e, f)_{\text{baseline}}$. We applied GLM analysis for the individual's CSD power difference $\Delta_{CSD}(e, f)$ at each frequency band at each edge with a design matrix composed of MDur and SI after Z-score normalization, plus a vector of one for offset, that is,

$$\Delta_{CSD}(e, f) = \beta_0 + \beta_1 \times MDur + \beta_2 \times SI. \quad (3)$$

Based on this GLM model, we explored the common(β_0), MDur(β_1), and SI(β_2) effects for longitudinal CSD changes. Although MDur and SI were significantly correlated ($r = 0.498$), the collinearity was not high enough. Thus, we did not conduct Gram-Schmidt orthogonalization.

3. Dynamic causal modeling of longitudinal EEG of chronic schizophrenia

To link neural properties at each hierarchical level with EEG, we modeled longitudinal EEGs of chronic patients with schizophrenia using DCM in the hierarchical Bayesian framework.

Figure 2 describes the entire procedure of the present work. 1) The EEG data were preprocessed to eliminate artifacts. 2) Using cross-spectral density (CSD) for DMN and AHN, we estimated individual-level full CMM-NMDA DCM models considering all potential extrinsic connections between brain regions in the network. 3) From estimated DCMs for individuals, we performed Bayesian model reduction and the best model selection for DMN and AHN. 4) Using the PEB method, we performed a group-level analysis to identify parameters for the group common, MDur, and SI effects. 5) Finally, we performed a virtual perturbation analysis to evaluate the effects of parameters on the CSD.

The current analysis is based on the CMM-NMDA model in `dcmm_meg` toolbox in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/SPM12/>). Figure 3 shows the hierarchical structure of a CMM-NMDAfor EEG model, which describes channel-level neural properties, interactions among subpopulations within a region, and interactions among the brain regions.

The current study follows the conventional DCM modeling (Friston et al., 2003), comprising a neural state model and an observation model. In the DCM, the neural state dynamics model $f(x(t), u(t), \theta)$ expresses the dynamics of neural states $x(t)$, that is, activities of neural populations. The observation model $h(x(t), \phi)$ converts the neural states $x(t)$ to the observed signals $y(t)$. The observed signals $y(t)$ can be formulated by the combination of the two model equations:

$$\dot{x} = f(x(t), u(t), \theta) + \Gamma_x, \quad (4)$$

$$y(t) = h(x(t), \phi) + \epsilon, \quad (5)$$

where θ and ϕ represent the model parameters for the neural state dynamics function f and the observation function g . $u(t)$ denotes an external stimulus or input, which is not specified in the modeling of resting-state EEG. Γ_x and ϵ represent endogenous fluctuation and observational noise.

3.1. CMM-NMDA neural state model

3.1.1. Intrinsic neural properties and dynamics

The CMM-NMDA model simulates neuronal activity in response to changes in the conductance of receptor channels. This model is composed of the conductance dynamics of three receptor channels, NMDA, AMPA, and gamma-aminobutyric acid (GABA) (Fig. 3A) (Pereira et al., 2021). The state dynamics of a neural population j with a neural state $x^{(j)} = \{\mu_V^{(j)}, \mu_{\text{gAMPA}}^{(j)}, \mu_{\text{gGABA}}^{(j)}, \mu_{\text{gNMDA}}^{(j)}\}$, is described as follows (Marreiros et al., 2009).

$$C^{(j)} \mu_V^{(j)} = \sum_k \mu_{\text{gk}}^{(j)} (V_k - \mu_V^{(j)}) + \mu_{\text{gNMDA}}^{(j)} m(\mu_V^{(j)}) (V_{\text{NMDA}} - \mu_V^{(j)}) \quad (6)$$

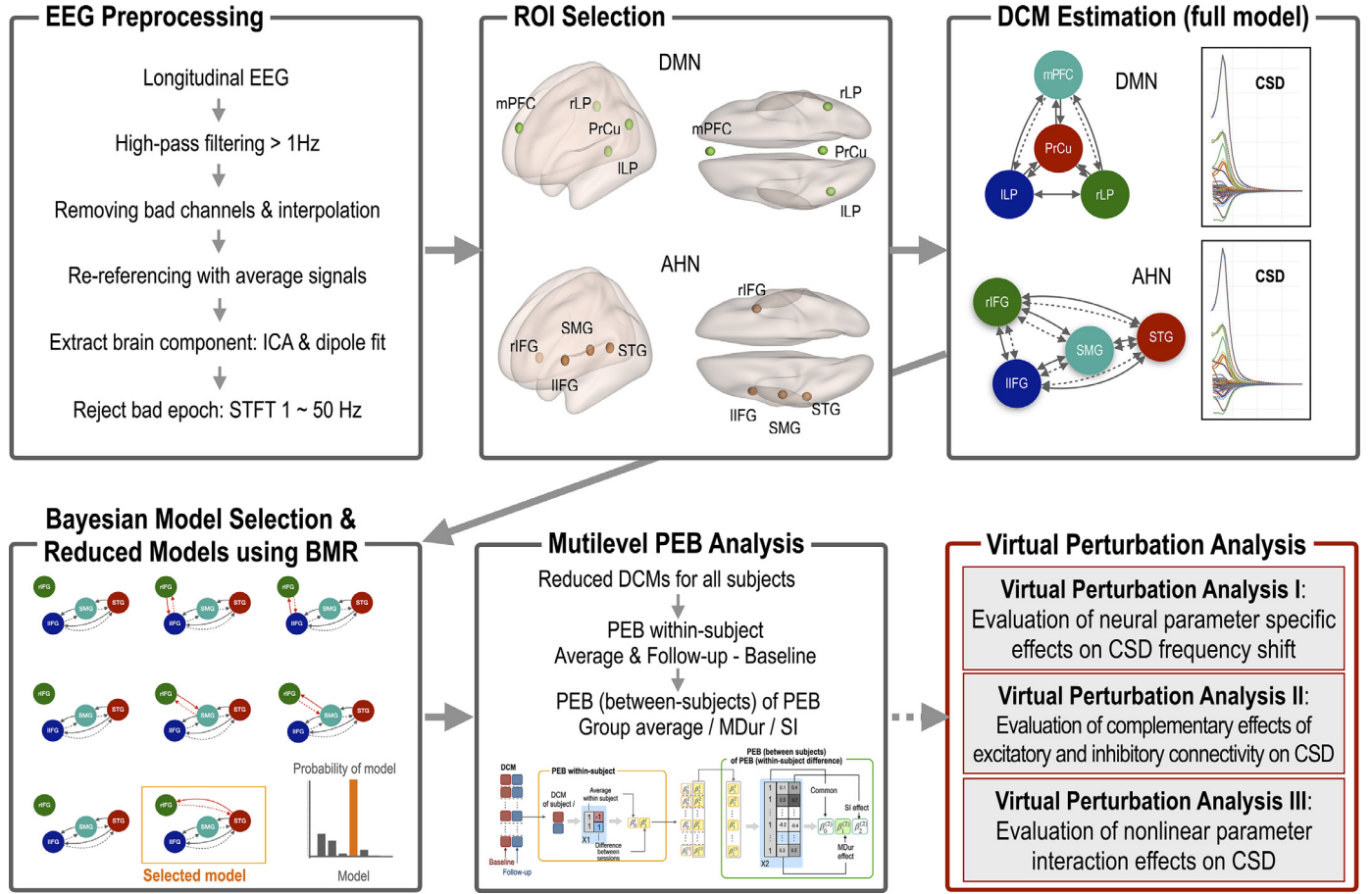


Fig. 2. The procedure of DCM PEB analysis for longitudinal neural property changes in patients with schizophrenia treated with clozapine. In the initial phase, the EEG data were preprocessed. We then selected regions of interest (ROI) for DMN and AHN, and estimated individual DCMs with full models, with all possible connections among regions in the network. For the estimated models, we conducted model reduction and selected the best models for DMN and AHN. The multilevel PEB analysis was applied to extract common, medication duration (MDur) and symptom improvement (SI)-related effects in neural property changes. Finally, we performed virtual perturbation analyses (for details, see Table 4).

$$\dot{\mu}_{gk}^{(j)} = \kappa_k^{(j)} \left(\tau_k^j - \mu_{gk}^{(j)} \right), \text{ for } k \in \{L, \text{AMPA}, \text{GABA}\}, \quad (7)$$

where $\mu_V^{(j)}$ represents the mean membrane voltage, and $\mu_{gk}^{(j)}$ the conductance of the channel k in the neural population j . Note that the conductance of the leak channel (denoted L), $\mu_{gL}^{(j)}$, is assumed to be a constant 1 as in SPM12. $m(\mu_V)$ reflects voltage-dependent magnesium (Mg^{+2}) block, which has a nonlinear relation with membrane voltage V (Jahr and Stevens, 1990; Koch, 1998; Moran et al., 2013a):

$$m(V) = \frac{1}{1 + 0.2 \cdot \exp(-\alpha_{\text{NMDA}} \cdot V)} \quad (8)$$

Here, α_{NMDA} is the magnesium block parameter set to 0.06 in SPM12.

3.1.2. Intrinsic connectivity

In the CMM-NMDA model, each brain region consists of four neural populations at three major cortical layers: the superficial pyramidal cell (sp), the spiny stellate cell (ss), the deep pyramidal cell (dp), and the inhibitory interneuron (ii) according to the columnar organization of the brain cortex (Fig. 3B). Connectivity between neural populations within a region is called intrinsic connectivity. Intrinsic connectivity from population i to j through channel k , is represented as a coupling parameter, $\gamma_k^{(i,j)}$, and the input to the j th neural population, ζ_k^j , is defined as below.

$$\zeta_k^j = \sum_i \gamma_k^{(i,j)} \sigma \left(\mu_V^i - V_R, \Sigma^i \right). \quad (9)$$

The function σ reflects the proportion of activated neurons in a neural population and is expressed as the cumulative distribution function of

the univariate normal distribution, with a mean ($\mu_V^i - V_R$) and variance Σ^i . V_R indicates the membrane potential threshold, which was set to -40mV in SPM12.

3.1.3. Extrinsic connectivity

The CMM-NMDA model contains both forward and backward connections mediated by AMPA and NMDA receptors, resulting in four types of extrinsic connections (Fig. 3C). Forward connectivity begins at the sp cell of a region and extends to the ss cell of its target region. Extrinsic backward connectivity begins with the dp cell of a region connecting to the sp and ii cells of its target region.

$$I_{k(i,j)}^f = A_{k(i,j)}^f \cdot \sigma_{j,sp} \quad (10)$$

$$I_{k(i,j)}^b = A_{k(i,j)}^b \cdot \sigma_{j,dp} \quad (11)$$

where $k \in \{\text{AMPA}, \text{NMDA}\}$

where $I_{k(i,j)}^f$ indicates the forward current in region j from region i , $I_{k(i,j)}^b$ the backward current, and $\sigma_{j,sp}$ and $\sigma_{j,dp}$ mean firing rate in the sp cell and in the dp cell. The details of the parameters are listed in Table 2.

3.2. EEG observation model

The observation model is a function that connects the activity of a source neural population to the sensor data. In the case of EEG, this

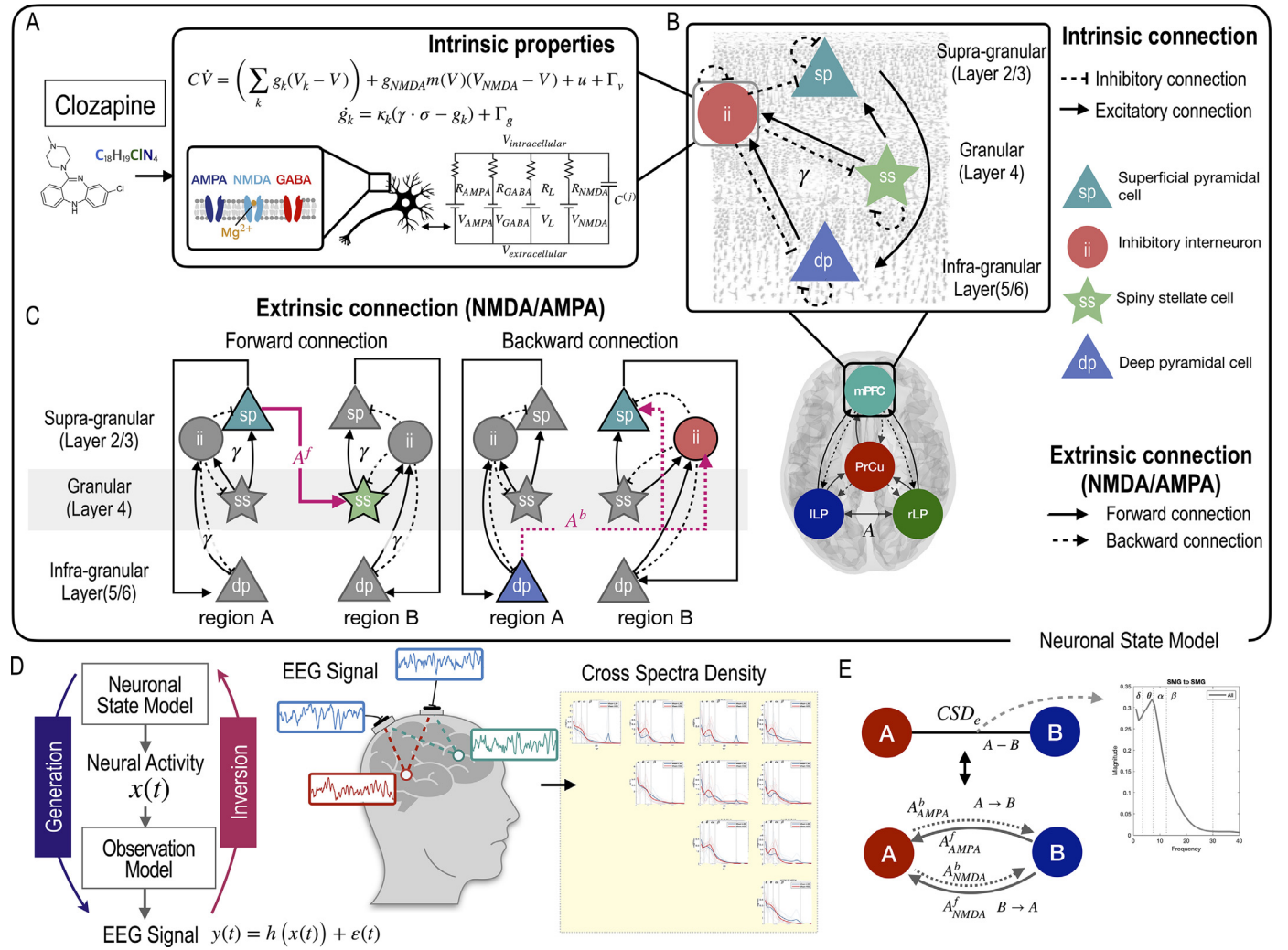


Fig. 3. The hierarchical structure of the CMM-NMDA model and model inversion using DCM. The CMM-NMDA model comprises intrinsic neural properties (A), intrinsic intra-regional connectivity (B), and extrinsic inter-regional connectivity (C). (A) The CMM-NMDA model describes dynamics in the membrane potential of a neural population according to conductance changes of three channels; NMDA, AMPA, and GABA channels. (B) Each brain region of the CMM-NMDA model is composed of four neuron populations, that is, superficial pyramidal (*sp*) cell, spiny stellate (*ss*) cell, deep pyramidal (*dp*) cell, and inhibitory interneuron (*ii*), which are interconnected via intrinsic connectivity (γ) in the model. (C) At the brain network level, pairs of two brain regions are connected via forward (A^f) or backward connections (A^b) (magenta solid and dotted lines), which are further classified as NMDA and AMPA connections. Thus, four extrinsic connections exist for pairs of two brain regions in the CMM-NMDA model. (D) In the DCM framework, the multiscale parameters of the CMM-NMDA involve in generating EEG signals through the neuronal state model and observation model. DCM inverts all model parameters to fit experimental cross-spectral density (CSD) derived from EEG. (E) The CSD edge component and the extrinsic connectivity for the CMM-NMDA model explain the same edge between regions A and B but differently. For an edge, a symmetric CSD is defined while eight extrinsic connectivity ($A_{AMPA}^f, A_{AMPA}^b, A_{NMDA}^f, A_{NMDA}^b$ for both directions of $A \rightarrow B, B \rightarrow A$) is defined in the CMM-NMDA model.

function is called the lead field or gain matrix $L(\phi)$ that maps the relationship between source positions and the sensor activity. The source is assumed to be the pyramidal cellular activity of a region.

$$\hat{y}_i(t) = h(x, \phi) = L(\phi)x(t) \quad (12)$$

$$y_i = \hat{y}_i + \varepsilon \quad (13)$$

where $\hat{y}_i$ and y_i represent the predicted and observed signals on a sensor i and $h(x, \phi)$ observation function, with measurement noise ε .

3.3. Model inversion

Using the variational Bayesian technique with the Laplace approximation (Friston et al., 2007; 2003), parameters in both the neural state and observation models were estimated from EEG data using SPM12. The model parameters were estimated by maximizing the free energy,

taking into account the accuracy and complexity of the model (Fig. 3D). We used cross-spectral density DCM (csd-DCM) analysis (Friston et al., 2012) for the resting state EEG in the absence of external stimuli. In csd-DCM, the CSD of the EEG data in the frequency range of 1 to 40 Hz was used to estimate the model parameters of the fully connected models (i.e., having all possible extrinsic connectivity) for DMN and AHN.

DCM estimates model parameters θ by maximizing the negative free energy, a function of observed data y and recognition density $q(\theta)$ as below:

$$F(q, y) = \langle \log p(y|\theta)_q \rangle - D_{KL}[q(\theta)||p(\theta)] \quad (14)$$

$p(y|\theta)$ is a likelihood function and D_{KL} represents Kullback-Leibler divergence between the recognition density $q(\theta)$ and the prior $p(\theta)$. When optimized, the recognition density $q(\theta)$ approximates the posterior $p(\theta|y)$.

Table 2
Summary of parameters.

Parameter	Description	Reference value	Prior
Intrinsic property			
α_{NMDA}	Magnesium block parameter	0.06	-
$C^{(j)}$	Membrane capacitance, $j \in \{ss, sp, ii, dp\}$	0.128, 0.128, 0.256, 0.032	$N(0, 1/16)$
S	Population variance	32	$N(0, 1/64)$
$T_{ch} (\sim 1/\kappa_{ch})$	Channel time constant [ms], $ch \in \{GABA, AMPA, NMDA\}$	4, 16, 100	$N(0, 1/64)$
E	Background activity	0.8	$N(0, 1/64)$
Intrinsic connectivity			
$\gamma_k(i \rightarrow j)$	Intrinsic connectivity from a neural population i to j in region k		
$\gamma_k(i \rightarrow j)$	$(i, j) \in \{(ss, sp), (ss, ii), (sp, dp)\}$	4	$N(0, 1/32)$
$\gamma_k(i \rightarrow j)$	$(i, j) \in \{(dp, ii), (ii, ss), (ii, dp)\}$	2	$N(0, 1/32)$
$\gamma_k(i \rightarrow j)$	$(i, j) \in \{(ii, dp), (ss, ss), (sp, sp)\}$	2	$N(0, 1/32)$
$\gamma_k(i \rightarrow j)$	$(i, j) \in \{(ii, ii)\}$	32	$N(0, 1/32)$
$\gamma_k(i \rightarrow j)$	$(i, j) \in \{(dp, dp)\}$	128	$N(0, 1/32)$
Extrinsic connectivity			
$A_{\text{NMDA}}^{f/b}(A \rightarrow B)$	NMDA extrinsic forward (f)/ backward (b) connectivity from region A to B	0.11	$N(0, 1/8)$
$A_{\text{AMPA}}^{f/b}(A \rightarrow B)$	AMPA extrinsic forward (f)/ backward (b) connectivity from region A to B	1	$N(0, 1/8)$

Notes: Unconnected edge in the reduced model is set by assigning the mean -32 with a covariance of 0 to the parameter of the full model. Prior distributions of all parameters, except T_{ch} , are given as $X = X_0 \exp(x)$, where $x \sim N(\text{mean}, \text{covariance})$, and prior distributions of T_{ch} parameters is given as $\kappa_{ch} = X_0 \exp(-x)$, where $x \sim N(\text{mean}, \text{covariance})$, $\kappa_{ch} = X_0 \exp(-x)$, where $x \sim N(\text{mean}, \text{covariance})$. X : parameter, X_0 : reference value. ch : channel type $\in \{GABA, AMPA, NMDA\}$. ss : excitatory spiny stellate cells; sp : excitatory superficial pyramidal cells; ii : inhibitory interneuron; dp : excitatory deep pyramidal cells.

As an index to the reliability of the estimated model, we used explained variance (EV):

$$EV = 100 \cdot \frac{\sum_{e,f} CSD(e, f)^2}{\sum_{e,f} CSD(e, f)^2 + \sum_{e,f} (CSD(e, f) - C\tilde{S}D(e, f))^2}. \quad (15)$$

Here, $CSD(e, f)$ and $C\tilde{S}D(e, f)$ denote the CSD of observed signals and the estimated CSD at frequency f at an edge e that connects two brain regions among a set of regions of the brain R (Fig. 3E).

The EVs for all patients were greater than 90% (average EV = 98.86 $\pm$ 0.96), indicating that the model reproduced the experimental data with high accuracy (Supplementary Figure S1).

3.4. Bayesian model selection for DMN and AHN

We selected the best model by performing Bayesian Model Selection (BMS) after generating various test models for DMN and AHN of all 23 patients' baseline and follow-up DCMs using Bayesian Model Reduction (BMR) (Friston and Penny, 2011; Friston et al., 2016; Zeidman et al., 2019). For this, we inverted the full DCM models with all possible edges among regions of each network using all EEG data. We then constructed various test models according to biological plausibility. The test model is a reduced model nested within the full model with the covariance of the to-be-reduced edge to zero. Among the biologically plausible test models, we performed BMS analysis and determined the best model for the group (Kass and Raftery, 1995; Stephan et al., 2010).

For DMN test models, based on Steen et al. (2019), we assigned the connection between LLP and rLP to be at the same hierarchical level and have forward and backward connections between them. Based on this constraint, 12 test models were generated by changing the backward and forward connections between mPFC, PrCu, and LP (see Supplementary Figure S2A). We selected the best model after performing BMS for these 12 test models (Fig. S3A).

AHN test models are constructed on the basis of Jardri et al. (2011). The basic hierarchy of the left hemisphere was set to IFG $\leftarrow$ SMG $\leftarrow$ STG. We also assigned direct connections from the STG to the lIFG and consider three types of connection from the three regions of the left brain with the right IFG (rIFG): absent, forward, and backward. Finally, 18 test models were generated using BMR (see Supplementary Figure S2B). We applied BMS to select the best model (Fig. S3B).

The best model for DMN in Fig. 4A sets the mPFC as the highest at the hierarchical level, followed by the PrCu and two LP regions. There are also direct connections from the two LP regions to the mPFC. In the

best model for AHN, rIFG appears to be hierarchically below lIFG but above SMG and STG (Fig. 4B). The probability of the best model in both networks is 1. (see Supplementary Figure S3)

3.5. Parametric empirical bayes: Multilevel analysis

PEB estimates group-level parameters according to the design matrix for the posterior density of the DCM parameters estimated at the individual level (Friston et al., 2015; 2016). More precisely, in the first-level DCM, the signal y_i of a patient i can be expressed by a function $\Gamma(\theta_i)$ of parameters θ_i and noise $\epsilon_i^{(1)}$. The DCM parameters estimated at the first level are modeled at the second level using a group design matrix X , the group effect β and the random effect $\epsilon^{(2)}$.

$$y_i = \Gamma(\theta_i) + \epsilon_i^{(1)} \quad (16)$$

$$\theta = X\beta + \epsilon^{(2)} \quad (17)$$

In the longitudinal data analysis, the PEB can be extended to third-level modeling for the second-level model parameters (Park et al., 2021; 2018; 2017). For example, the longitudinal effect in the first-level DCM parameters of an individual can be modeled at the second level (between-session within-subject). The longitudinal effect between sessions of each individual can be further modeled at the third group level (between subjects).

In the current study, we modeled the between-session effect (follow-up versus baseline) of an individual with a second-level design matrix, $X_1 = [1 \ 1; 1 \ -1]$ (Fig. 5). The second between-session effect (that is, the difference between follow-up and baseline) of group individuals was again modeled with MDur and SI of individuals as regressors in the third-level design matrix X_2 , after Z-score normalization. This PEB analysis resulted in the group-level parameters for the common, MDur, and SI effects. The common effect implies the average amount of longitudinal parametric changes between individuals, after adjusting to the mean MDur and the mean SI since MDur and SI were centered. The group-level design matrix X_2 is the same as that used in the CSD GLM analysis in the previous Section 2.4.

In the subsequent analysis, we focus on three types of parameters at different hierarchical levels: intrinsic neural properties (membrane capacitance C^i and channel decay time constant T_{ch}); intrinsic connectivity coefficient ($\gamma_k(i \rightarrow j)$); extrinsic AMPA/NMDA connectivity of AMPA and NMDA ($A_{\text{AMPA/NMDA}}^{f/b}$).

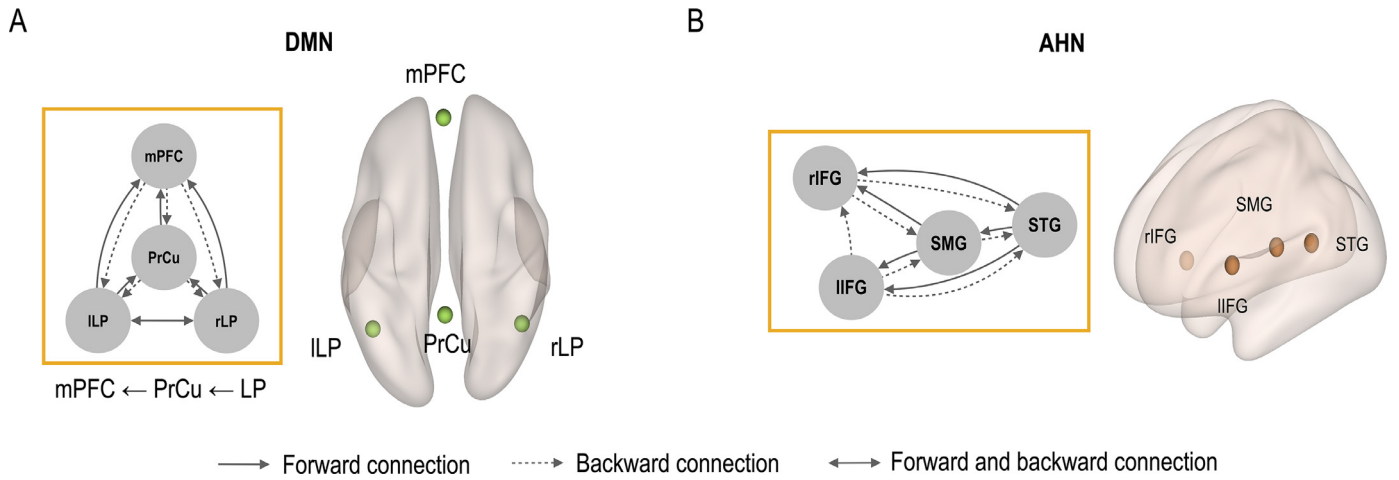


Fig. 4. The best models for the default mode network (DMN) and the auditory verbal hallucinations network (AHN) based on Bayesian model selection (BMS). ILP: left lateral parietal lobe; rLP: right lateral parietal lobe; PrCu: middle posterior cingulate/precuneus; mPFC: medial prefrontal cortex; IIFG: left inferior frontal gyri; rIFG: right inferior frontal gyrus; STG: left superior and middle temporal gyrus; SMG: left supramarginal gyrus.

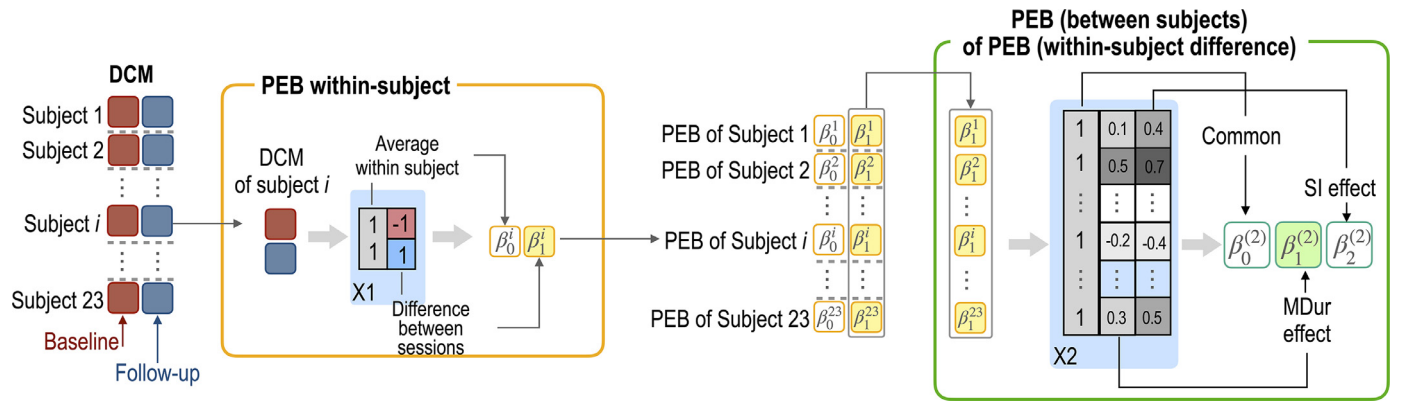


Fig. 5. Procedure for two-step PEB analysis. In the first step, a within-subject PEB analysis (or the second-level analysis) was applied to the DCMs of each patient estimated at the first level. The design matrix of this PEB analysis, X1, includes the average and difference between baseline and follow-up DCMs. In the second step, an additional PEB (third-level analysis) was applied to the second term (difference between sessions) of within-subject PEB results of individuals. The design matrix in this step, X2, includes the average, medication duration (MDur), and symptom improvement ratio (SI).

4. Analysis results

4.1. GLM analysis results: Main effects of MDur and SI for longitudinal CSD changes

The differential effects of MDur and SI on $\Delta_{CSD}(e, f)$ in all 23 patients, that is, the longitudinal changes of CSD between follow-up and baseline, according to frequency bands and networks, are shown in Fig. 6 and Supplementary Table S1.

The common effects of the longitudinal changes in CSD are more prominent in DMN than in AHN. In DMN, the negative longitudinal difference (follow-up versus baseline) of CSD in the delta band and the positive difference in the alpha band were found at almost all edges. The theta band CSD between the mPFC and ILP showed a longitudinal increase in the group common effect. As the medication duration increases, the longitudinal increase ($\Delta_{CSD}(e, f)$) decreases more at the theta band of ILP-ILP and mPFC-mPFC and the delta band of PrCu-rLP. In contrast, longitudinal differences in the alpha band of rLP-rLP, the beta band of mPFC-mPFC, and the beta band in CSD of rLP-mPFC increased along with the increased duration. The difference in the beta band CSD between the ILP and rLP increases proportionally to increased SI.

In AHN, the edges of the common group difference in CSD do not appear significant. The alpha frequency band in SMG-IIFG, SMG-STG, rIFG-SMG, and rIFG-STG, and the beta frequency band in IIFG-STG showed

positive effects of MDur. As SI increases, both IIFG and STG show a longitudinal decrease in theta frequency power, but an increase in the beta frequency power in IIFG. Longitudinal differences in interhemispheric CSD between IIFG and rIFG, and between SMG and rIFG in theta band showed a negative effect of SI. The interaction between the hemispheres is predominant in MDur and SI of both DMN and AHN, indicating that medication durations and symptomatic improvements of the individuals are closely related to hemispheric interactions.

4.2. PEB analysis results: Main effects of MDur and SI for longitudinal changes on model parameters

PEB analysis reveals parameter sets associated with the common, MDur and SI effects in DMN and AHN. The model parameters that survived a non-zero criterion with a posterior confidence of 95% are shown in Fig. 7 and Supplementary Figure S4, and are summarized in Table 3.

The common, MDur, and SI effects were found at different hierarchical levels. These include intrinsic neural properties, intrinsic connectivity, and extrinsic interregional connectivity.

In the common effect, that is, the average group difference in the parameter between follow-up and baseline, most parameters decreased in both DMN and AHN. However, the intrinsic connection for $ss \rightarrow sp$ in the mPFC ($\gamma_{mPFC}(ss \rightarrow sp)$) and rLP ($\gamma_{rLP}(ss \rightarrow sp)$) of DMN and $ii \rightarrow dp$ in the STG ($\gamma_{STG}(ii \rightarrow dp)$) of AHN shows a longitudinal increase.

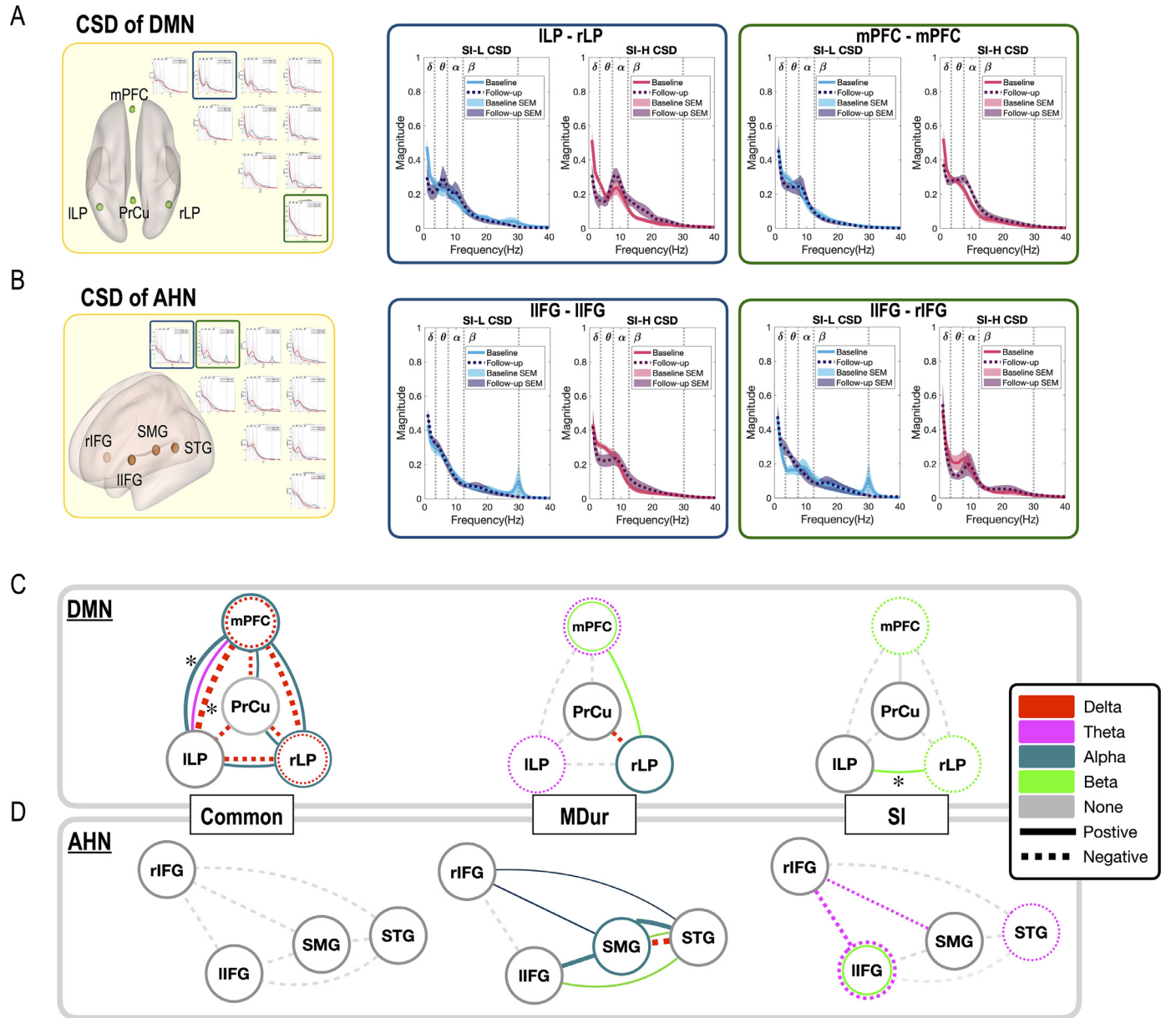


Fig. 6. GLM analysis results for longitudinal CSD differences at four frequency bands in all 23 patients. All patients' symptom improvement ratio (SI) and medication duration (MDur) were associated with the CSD differences using GLM analysis. (A-B) The exemplary CSDs at the edges related to the symptom improvement ratio (SI) in (A) DMN and (B) AHN are displayed separately for the SI-L (blue) and SI-H (red) groups despite no statistical group test in this experiment. Solid lines and dashed lines indicate the average CSDs of each group for baseline and follow-up. The light-colored shadow represents the standard error of the mean of each group ($n = 8$). (C-D) CSDs related to the common, medication duration (MDur), and SI effects for each frequency band for DMN (C) and AHN (D) are displayed. Solid colored lines and dashed lines represent positive and negative effects ($p < 0.05$) for each frequency band. Circles represent the effects associated with the power spectrum. The asterisks indicate the significance of the edges after the Bonferroni correction with factor 40 (4 frequency bands $\times$ 10 non-duplicated edges of a 4×4 symmetric matrix). DMN: default mode network; ILP: left lateral parietal lobe; rLP: right lateral parietal lobe; PrCu: middle posterior cingulate/precuneus; mPFC: medial prefrontal cortex; AHN: auditory verbal hallucinations network; IIFG: left inferior frontal gyrus; rIFG: right inferior frontal gyrus; STG: left superior and middle temporal gyri; SMG: left supramarginal gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The MDur effects were found mainly in the intrinsic connectivity associated with inhibitory cells *ii*. Meanwhile, SI effects were found at membrane capacitance and intrinsic connectivity in DMN and intrinsic connectivity and extrinsic connectivity in AHN. Regarding intrinsic properties, PEB identified a reduced membrane capacity $C^{(dp)}$ of the deep pyramidal cell for SI in DMN and an increased NMDA time constant in the left and right LPs for MDur.

In both DMN and AHN, only a few extrinsic connectivities were identified as significant in PEB.

In DMN, a significantly reduced longitudinal alteration was found from baseline to follow-up in forward connectivity $A_{AMPA}^f(ILP \rightarrow rLP)$ and backward connectivity $A_{AMPA}^b(ILP \rightarrow rLP)$. In AHN, an SI-related increase was found in AMPA connectivity from STG to IIFG ($A_{AMPA}^f(STG \rightarrow IIFG)$).

Note that each edge e has a value $CSD(e, f)$ at the level of the EEG CSD, and the forward and backward model parameters, $A_{NMDA}^{f/b}(e)$ and $A_{AMPA}^{f/b}(e)$, as shown in Fig. 3E. However, the changes in longitudinal parameters associated with common, MDur, and SI do not overlap

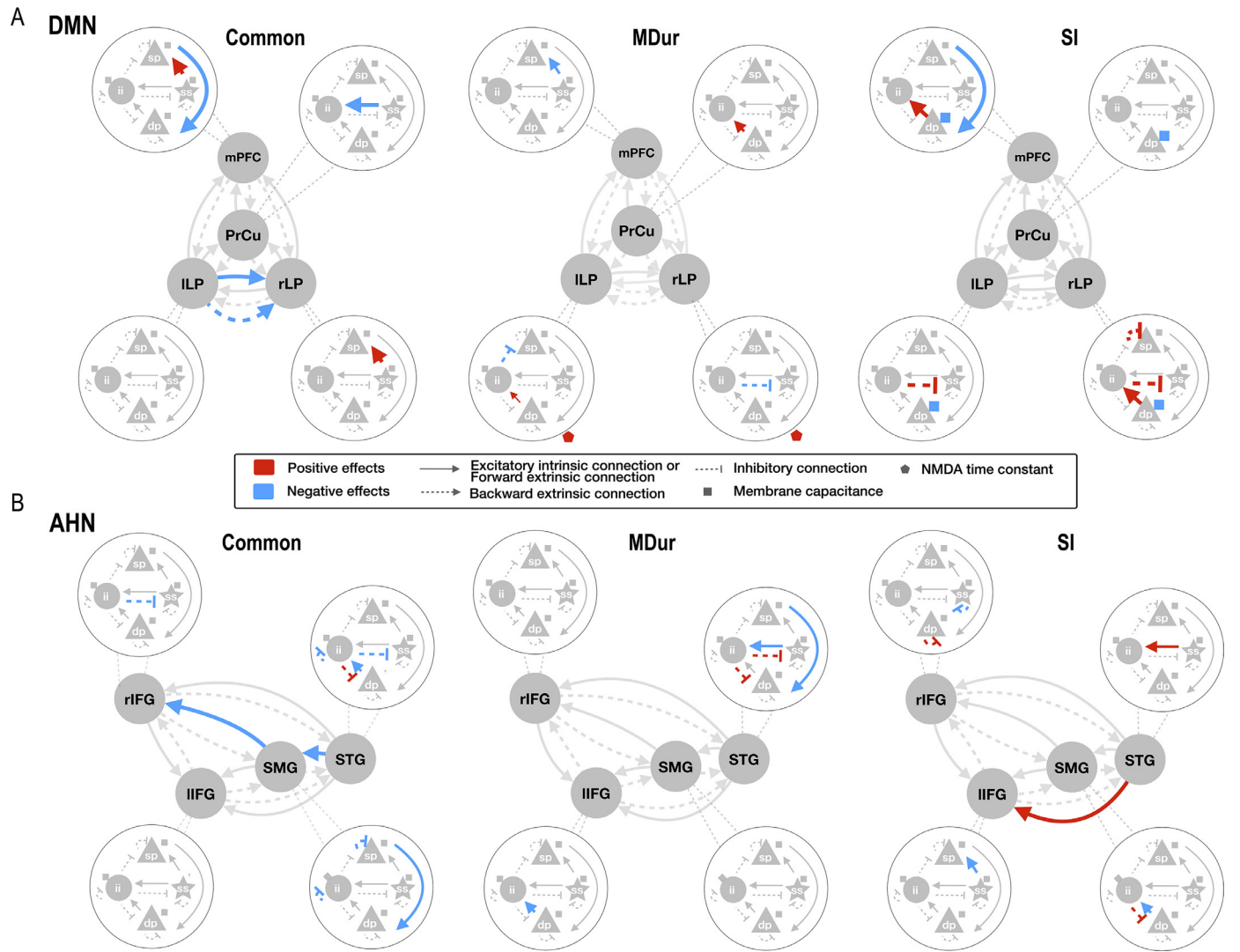


Fig. 7. Results of the PEB analysis. Significant parameters (i.e., 95% of credible intervals of parameters are outside zero) for the common, medication duration (MDur), and symptom improvement ratio (SI) effects are displayed for DMN (A) and AHN (B). Red and blue represent positive and negative effects. The solid and dashed lines represent forward and backward connectivity for extrinsic connections, and excitatory and inhibitory connectivity for intrinsic connections. The width of the line represents the strength of the connection. Here, all significant extrinsic connections were AMPA connections. Intrinsic neural properties such as the channel time constant (τ) and the membrane potential (C) are displayed with a pentagon and a square. DMN: default mode network; ILP: left lateral parietal lobe; rLP: right lateral parietal lobe; PrCu: middle posterior cingulate/precuneus; mPFC: medial prefrontal cortex; AHN: auditory verbal hallucinations network; IIFG: left inferior frontal gyrus; rIFG: right inferior frontal gyri; STG: left superior and middle temporal gyrus; SMG: left supramarginal gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

closely with those of longitudinal changes in edges in the CSD power (Figs. 6–7).

5. Virtual perturbation analysis I. The parameter specific effects on CSD frequency shift

To analyze the parameter-specific effects on CSD, we conducted virtual perturbation analyses for different purposes, which are summarized in Table 4. The basic notation for the virtual perturbation analysis is shown in the upper part of Table 4. Note that the previous PEB results were used only in Perturbation 1 of Virtual Perturbation Analysis I in Table 4, while all model parameters were evaluated afterward.

5.1. Sensitivity of parameters on altering frequency specific CSD

We explored the sensitivity of each model parameter in inducing follow-up CSD. For this, we replaced the target parameters of the baseline with those of the follow-up system and generated a simulated

$CSD(e, f)$, denoted as $\tilde{CSD}(e, f)$, for all frequency bands f at each edge e . To emphasize the frequency shifts between the two acquisitions, we calculated the individual's relative CSD power, denoted as $rCSD(e, f)$, which is the CSD power of a frequency band f divided by the sum of all frequencies in an edge e .

$$rCSD(e, f) = \frac{CSD(e, f)}{\sum_f CSD(e, f)} \quad (18)$$

We defined the degree of frequency shift or sensitivity $\Delta_{rCSD}^{(p)}(e, f)$ of a parameter (p) (Fig. 8) by calculating the difference between the relative CSD powers of the simulated $\tilde{CSD}$ and the baseline CSD. The simulated CSD ($\tilde{CSD}$) was generated by a virtual model after replacing the baseline parameter with that of the follow-up.

$$\Delta_{rCSD}^{(p)}(e, f) = rCSD(e, f | \{\Theta_p^{(1)}, \Theta_p^{(2)}\}) - rCSD^{(1)}(e, f) \quad (19)$$

which indicates the deviation of the estimated relative CSD (rCSD) from the baseline rCSD by replacing a baseline parameter with that of the follow-up.

Table 3
PEB analysis results.

DMN					
Common	β_0	Duration (MDur)	β_1	Improvement (SI)	β_2
$A_{AMPA}^f(ILLP \rightarrow rLP)$	-0.2228	$T_{NMDA}(ILLP)$	0.0999	$C^{(dp)}$	-0.2414
$A_{AMPA}^b(ILLP \rightarrow rLP)$	-0.2245	$T_{NMDA}(rLP)$	0.1005	$\gamma_{ILLP}(ii \rightarrow ss)$	0.1273
$\gamma_{rLP}(ss \rightarrow sp)$	0.1826	$\gamma_{ILLP}(ii \rightarrow sp)$	0.1767	$\gamma_{rLP}(sp \rightarrow sp)$	0.1371
$\gamma_{PrCu}(ss \rightarrow ii)$	-0.1392	$\gamma_{rLP}(ii \rightarrow ss)$	-0.2176	$\gamma_{rLP}(ii \rightarrow ss)$	0.2326
$\gamma_{mPFC}(ss \rightarrow sp)$	0.1132	$\gamma_{PrCu}(dp \rightarrow ii)$	0.1813	$\gamma_{rLP}(dp \rightarrow ii)$	0.1588
$\gamma_{mPFC}(sp \rightarrow dp)$	-0.1243	$\gamma_{mPFC}(ss \rightarrow sp)$	-0.1623	$\gamma_{mPFC}(sp \rightarrow dp)$	-0.1721
				$\gamma_{mPFC}(dp \rightarrow ii)$	0.1362
AHN					
Common	β_0	Duration (MDur)	β_1	Improvement (SI)	β_2
$A_{AMPA}^f(STG \rightarrow SMG)$	-0.2287	$\gamma_{IFG}(dp \rightarrow ii)$	-0.1376	$A_{AMPA}^f(STG \rightarrow IIFG)$	0.2894
$A_{AMPA}^b(SMG \rightarrow rIFG)$	-0.2076	$\gamma_{STG}(ss \rightarrow ii)$	-0.1436	$\gamma_{IFG}(ss \rightarrow sp)$	-0.1107
$\gamma_{rIFG}(ii \rightarrow ss)$	-0.1451	$\gamma_{STG}(sp \rightarrow dp)$	-0.126	$\gamma_{rIFG}(ss \rightarrow ss)$	-0.1838
$\gamma_{STG}(ii \rightarrow ss)$	-0.183	$\gamma_{STG}(ii \rightarrow ss)$	0.1821	$\gamma_{rIFG}(dp \rightarrow dp)$	0.1318
$\gamma_{STG}(ii \rightarrow ii)$	-0.1307	$\gamma_{STG}(ii \rightarrow dp)$	0.1627	$\gamma_{STG}(ss \rightarrow ii)$	0.1293
$\gamma_{STG}(ii \rightarrow dp)$	0.181			$\gamma_{SMG}(ii \rightarrow dp)$	0.1365
$\gamma_{STG}(dp \rightarrow ii)$	-0.1228			$\gamma_{SMG}(dp \rightarrow ii)$	-0.1223
$\gamma_{SMG}(sp \rightarrow sp)$	-0.1367				
$\gamma_{SMG}(sp \rightarrow dp)$	-0.1111				
$\gamma_{SMG}(ii \rightarrow ii)$	-0.1071				

$A_{AMPA}^{f/b}(A \rightarrow B)$: AMPA extrinsic forward (f)/ backward (b) connectivity from region A to B; $\gamma_k(i \rightarrow j)$: Intrinsic connectivity from a neural population i to j at region k ; $C^{(i)}$: Membrane capacitance, AMPA extrinsic forward (f)/ back- ward (b) connectivity from region A to B;

Table 4
Summary for Virtual Perturbation Analyses.

Notation	
$\Theta^{(t)}$	Parameters at the time t
t	Acquisition time t ($t = 1$ for baseline, $t = 2$ for follow-up)
$\Theta^{(i)}$	Subset of $\Theta^{(i)}$ composed of parameters belonging to a parameter subset p
$\Theta_p^{(i)}$	Subset of $\Theta^{(i)}$ composed of all parameters except the parameter subset p
$CSD^{(i)}(e, f)$	Empirical CSD power at the frequency (bands) of f at the edge e at time t
$C\tilde{S}D^{(i)}(e, f \Theta^{(i)})$	Simulated CSD power at frequency (bands) of f at edge e at time t using $\Theta^{(i)}$
Virtual Perturbation Analysis I: Sensitivity of parameters on altering frequency specific CSD	
Perturbation 1	Sensitivity of parameters (Fig. 8)
• Parameter	$\{\Theta_{\{p\}}^{(1)}, \Theta_{\{p\}}^{(2)}\}$, $p \in \{\text{significant PEB parameter displayed in Table 3 and Fig. 7}\}$.
• Evaluation	$\Delta_{CSD}^{(p)}(e, f) = rC\tilde{S}D(e, f \{\Theta_{\{p\}}^{(1)}, \Theta_{\{p\}}^{(2)}\}) - rCSD^{(1)}(e, f)$ (Eq. (19)).
• Patient	All patients
Perturbation 2	Contribution of parameter sets on the CSD change (Fig. 9)
• Parameter	$\{\Theta_{\{c\}}^{(2)}, \Theta_{\{c\}}^{(1)}\}$, $c = \{ip, ic, ec\}$. ip : intrinsic property category set ic : intrinsic connectivity category set ec : extrinsic connectivity category set
• Evaluation	$\Delta_{rCSD}^{(c)}(e, f) = rC\tilde{S}D(e, f \{\Theta_{\{c\}}^{(2)}, \Theta_{\{c\}}^{(1)}\}) - rCSD^{(2)}(e, f)$, $c \in \{ip, ic, ec\}$ (Eq. (20)).
• Patient	All patients
Virtual Perturbation Analysis II: Complementary effects of excitatory and inhibitory connectivity on CSD	
Perturbation 3	Interdependency of excitatory and inhibitory connectivity on CSD (Fig. 10)
• Parameter	$\{\Theta_{\{E, I\}}^{(2)}, \Theta_{\{E\}}^{(2)} + \lambda_E \Delta \Theta_E, \Theta_{\{I\}}^{(2)} + \lambda_I \Delta \Theta_I\}$ (Eq. (21))
• Evaluation	$\Delta_{rCSD}(e, f \lambda_E, \lambda_I) = rC\tilde{S}D(e, f \{\Theta_{\{E\}}^{(2)}, \Theta_{\{I\}}^{(2)}\}) - rCSD^{(2)}(e, f)$ (Eq. (22)).
• Patient	Patients in SI-H group
Virtual Perturbation Analysis III: Core parameters and nonlinear parameter interactions on CSD progression	
Perturbation 4	Analysis of CSD trajectories and prediction of CSD progression (Fig. 11)
• Parameter	$\{\Theta_{\{all\}}^{(1)} + \lambda(\Theta_{\{all\}}^{(2)} - \Theta_{\{all\}}^{(1)})\}$ (Eq. (23))
• Evaluation	$C\tilde{S}D$ pattern.
• Patient	Patients in the SI-H group
Perturbation 5	Core parameters for CSD progression (Fig. 12)
• Parameter	$\{\Theta_{\{p\}}^{(2)}, \Theta_{\{p\}}^{(2)} + \log(1.5) \cdot \text{sign}(\Theta_{\{p\}}^{(2)} - \Theta_{\{p\}}^{(1)})\}$ (Eq. (24))
• Evaluation	$RMS E_p = \sqrt{\frac{1}{m(E) \times n(F)} \sum_{e \in E} \sum_{f \in F} \{C\tilde{S}D(e, f \Theta^{(p)}) - CSD^{(2)}(e, f)\}^2}$ (Eq. (27)).
• Patient	Patients in the SI-H group
Perturbation 6	Nonlinear interactions effects of parameters on CSD progression (Fig. 14)
• Parameter	$\{\Theta_{\{p_1, p_2\}}^{(2)}, \Theta_{\{p_1, p_2\}}^{(2)} + \log(1.5) \cdot \text{sign}(\Theta_{\{p_1, p_2\}}^{(2)} - \Theta_{\{p_1, p_2\}}^{(1)})\}$ (Eq. (26))
• Evaluation	$I(p_1, p_2) = 1, -1, 0$ for positive, negative, mild synergistic interactions (Eq. (28)).
• Patient	Patients in the SI-H group

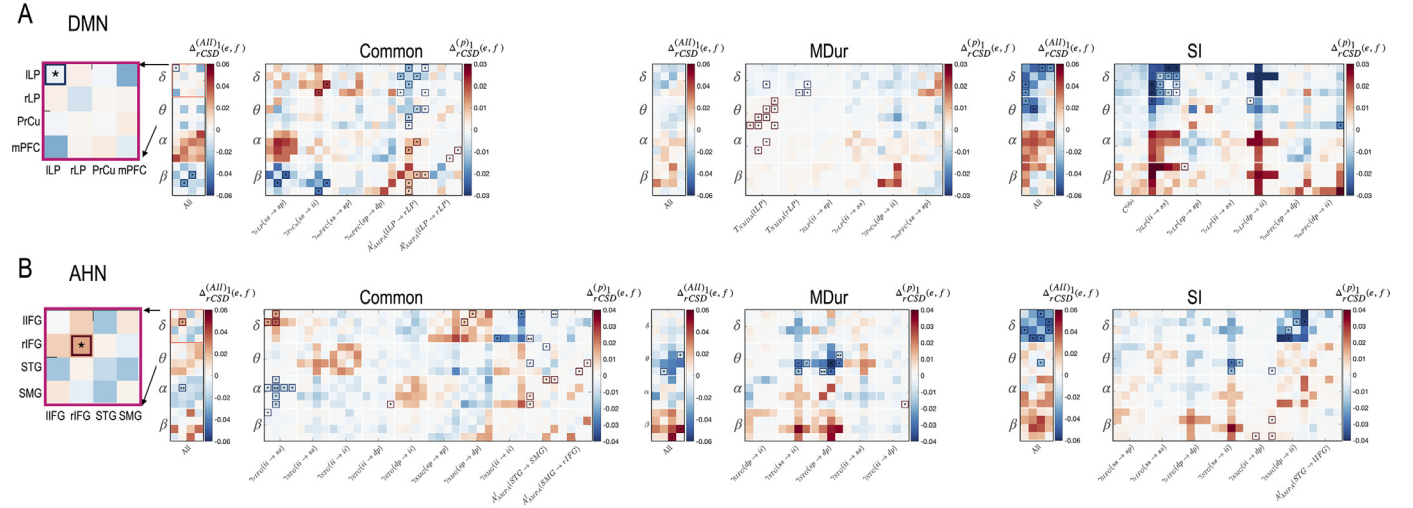


Fig. 8. Effects of model parameters on CSD edges, evaluated using $\Delta_{rCSD}^{(p)}(e, f)$ for each parameter p , in DMN (A) and AHN (B). $\Delta_{rCSD}^{(p)}(e, f)$ indicates the relative power difference after replacing a specific parameter with the follow-up from baseline. This measure indicates the parameter's contribution to the deviation from the baseline. The group averages of $\Delta_{rCSD}^{(p)}(e, f)$ for each parameter p or for all parameters in the set of parameters with significant effects associated with the common, medication duration (MDur), and SI in the previous PEB analysis is displayed for each frequency band (δ, θ, α , and β) and each parameter indicates $\Delta_{rCSD}^{(p)}(e, f)$ for all edges of the network, either DMN (A) or AHN (B). The brain regions are listed in the zoomed examples. The dots within the red and blue boxes represent the positive and negative changes that were found to be statistically significant in a one-sample t -test (one asterisk: $p < 0.05$, two asterisks: $p < 0.01$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We evaluated the sensitivity to frequency shift of each parameter in a set of significant effects for common, MDur, and SI in the PEB analysis (Table 3 and Fig. 7). Figure 8 presents the results of this perturbation analysis showing the average frequency shift patterns of the group at the CSD edges in DMN and AHN.

In DMN (Fig. 8A), the alternation from baseline to follow-up at $A_{AMPA}^f(1LP \rightarrow rLP)$ plays a dominant role in altering baseline CSD, by reducing slow interaction components (δ, θ band frequencies) but increasing fast interaction components (α, β band frequencies). The forward connection $A_{AMPA}^f(1LP \rightarrow rLP)$ reduced $\Delta_{rCSD}(1LP - rLP, \delta)$, while the backward connection $A_{AMPA}^b(1LP \rightarrow rLP)$ tends to increase $\Delta_{rCSD}(1LP - rLP, \delta)$. $T_{NMDA}(1LP)$ in the MDur effect parameter set increased theta band interactions of most CSD edges, not only the 1LP-connected edges. $\gamma_{1LP}(ii \rightarrow ss)$, an SI-related parameter, reduced delta band interactions at most CSD edges.

In AHN (Fig. 8B), a parameter related to the common effect, $\gamma_{rIFG}(ii \rightarrow ss)$, increased the delta-band CSDs of rIFG-IIFG and rIFG-rIFG, but reduced alpha band CSDs between rIFG and all other regions. $\gamma_{STG}(sp \rightarrow dp)$ and $\gamma_{STG}(ss \rightarrow ii)$, two parameters related to MDur, reduced slow-frequency CSDs while increasing high-frequency CSDs. Among the parameters related to SI, $\gamma_{SMG}(dp \rightarrow ii)$ reduced the delta band CSD between SMG and STG, while $\gamma_{SMG}(ii \rightarrow dp)$ increased the beta band CSD between SMG and rIFG.

5.2. Contribution of intrinsic property, intrinsic connectivity and extrinsic connectivity on the CSD change

We analyzed the contribution of each parameter set (categorized into intrinsic properties, intrinsic connectivity, and extrinsic connectivity) by evaluating the deviation of the relative CSD (rCSD) from the follow-up rCSD due to the replacement of a set of parameters c from the follow-up with that of the baseline.

$$\Delta_{rCSD}^{(c)}(e, f) = rCSD(e, f | \{\Theta_e^{(2)}, \Theta_e^{(1)}\}) - rCSD^{(2)}(e, f), \quad c \in \{ip, ic, ec\} \quad (20)$$

This evaluation differs from $\Delta_{rCSD}^{(p)}(e, f)$ in Eq. (19), which starts from the baseline model.

DMN and AHN show different deviations in these parameter sets (Fig. 9). The intrinsic property contributed greatly to the alpha fre-

quency band of rCSD, while the intrinsic connectivity contributes mainly to theta and beta frequency bands in AHN. In general, intrinsic connectivity induced more frequency shifts than extrinsic connectivity. In DMN, extrinsic connectivity showed opposite trends in the delta and alpha bands and the theta and beta bands, but changes were minimal. In AHN, the contribution of intrinsic connectivity was outstanding, generally reducing the delta- and theta-band CSDs and increasing the beta-band CSDs. Intrinsic properties show high contributions for alpha-band CSDs.

6. Virtual perturbation analysis II. Complementary effects of excitatory and inhibitory connectivity on CSD change

To investigate the effects of excitatory and inhibitory connectivity on CSD in the SI-H group (relatively long medicated and showing improved symptom scores), we divided all intrinsic connectivity into two connectivity sets: intrinsic connections from an inhibitory subpopulation ii to other subpopulations (called I-edges) and all excitatory connections from non-inhibitory subpopulations to other subpopulations (E-edges).

We altered each type of connectivity set by increasing or decreasing them according to the proportion of the parameter difference between follow-up and baseline.

$$\tilde{\Theta}^{(d)}(\lambda_E, \lambda_I) = \{\Theta_{(E \cup I)}^{(2)}, \Theta_E^{(2)} + \lambda_E \Delta \Theta_E, \Theta_I^{(2)} + \lambda_I \Delta \Theta_I\} \quad (21)$$

$$\lambda_E, \lambda_I \in \{-1.5, -1.4, \dots, 1.4, 1.5\}$$

where $\Delta \Theta_{E/I} = \Theta_{E/I}^{(1)} - \Theta_{E/I}^{(2)}$ is a difference vector between the baseline and follow-up parameters.

We then evaluated the deviation of the relative CSD from the follow-up by calculating the mean of the relative power difference between the simulated rCSD and that of the follow-up.

$$\Delta_{rCSD}(f | \lambda_E, \lambda_I) = \sum_e \left\{ rCSD(e, f | \tilde{\Theta}_e^{(d)}(\lambda_E, \lambda_I)) - rCSD^{(2)}(e, f) \right\} \quad (22)$$

Figure 10 shows the landscape of the rCSD deviation from the follow-up (i.e., the absolute value of $\Delta_{rCSD}(f | \lambda_E, \lambda_I)$) as a function of intrinsic excitatory (λ_E) and inhibitory connectivity strength (λ_I) as two axes. The effects of excitatory and inhibitory connectivity strengths on CSD

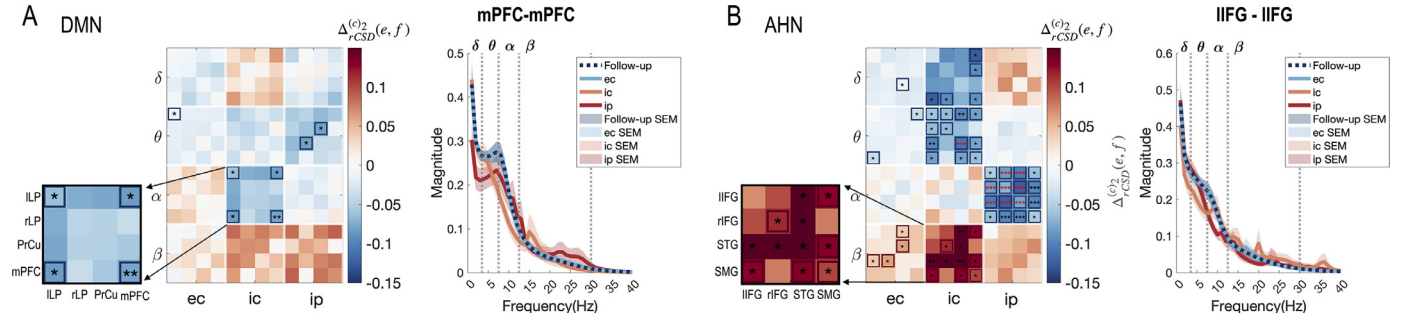


Fig. 9. Effect of parameter sets of extrinsic connectivity (ec), intrinsic connectivity (ic), and intrinsic neural property (ip) on CSDs in DMN (A) and AHN (B), evaluated using $\Delta_{rCSD}^{(e)}(e, f)$. $\Delta_{rCSD}^{(e)}(e, f)$ indicates the relative CSD deviation from the relative follow-up CSD due to the replacement of a parameter set e of the follow-up with that of the baseline. The group average $\Delta_{rCSD}^{(e)}(e, f)$ was displayed with a statistical significance mark within the red and blue boxes in a one-sample t -test (one asterisk: $p < 0.05$, two asterisks: $p < 0.01$, three asterisks: $p < 0.005$, three asterisks with red: Bonferroni correction passed). The group average CSDs at the baseline and after replacing each parameter set, i.e., ec , ic , and ip , were exemplarily displayed. The light-colored shadow represents the standard error ($n = 23$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

frequency shifts differ depending on the frequency bands and networks. In DMN, the low-frequency band (δ and θ) rCSDs of the baseline system remarkably get close to the follow-up system (colored blue) as excitatory and inhibitory connectivity increased to the level of follow-up. Further increases in excitatory and inhibitory connectivity beyond the level of the follow-up did not induce notable shifts in low-frequency CSD in DMN. A black-lined white region in Fig. 10 indicates a stable parameter zone for rCSD generation where simulated rCSD does not significantly deviate from the follow-up rCSD. If the excitatory and inhibitory connectivity strength remains within this stable zone, the rCSDs do not differ substantially from the follow-up system. The alpha frequency band rCSD in DMN has a narrow-shaped stable zone, indicating the balance between excitatory and inhibitory connectivity strengths to stay within this stable zone. In the beta frequency band in DMN, the inhibitory connectivity strength is critical for rCSD shift but is less dependent on the excitatory connectivity strength. In the AHN, the excitatory and inhibitory pattern in the delta-band rCSD was similar to that of the DMN delta frequency band. The stable zone of the theta band in AHN is fairly similar to that of the alpha band in DMN, located between the increase and decrease of frequency-specific rCSD.

7. Virtual perturbation analysis III. Core parameters and nonlinear parameter interactions on CSD progression

7.1. Analysis of CSD trajectories and prediction of CSD progression

By using a generative model in the CMM-NMDA, we explored a CSD evolution trajectory from baseline to follow-up for each individual in the SI-H group. For this evaluation, we assumed that the unit change of the parameter set is proportional to the difference vector between the follow-up and baseline parameters. We also predicted the CSD progression after follow-up by extrapolating parameters according to this difference vector.

$$C\tilde{S}D(e, f) = C\tilde{S}D(e, f | \{\Theta^{(1)} + \lambda(\Theta^{(2)} - \Theta^{(1)})\}) \quad (23)$$

$$\lambda \in \{0, 0.25, 0.5, 0.75, 1, 1.25\}$$

Here, λ simulates the time points on the trajectory from baseline to follow-up. $\lambda = 0$ and $\lambda = 1$ generate CSDs with baseline and follow-up parameters. $\lambda = 1.25$ correspond to the future time point with extrapolated parameters after follow-up.

The simulation results of four patients (S11 and S4 in the SI-L group and S2 and S17 in the SI-H group) are shown in Fig. 11, which shows the heterogeneous time courses of CSDs from baseline to follow-up across patients and networks. For example, in DMN, S11 and S2 showed shifts of complex CSD peaks along the time course to follow-up. In contrast, the spectral peaks and amplitudes in AHN gradually shifted. Consequently,

CSD after follow-up with $\lambda = 1.25$ can be easily predicted for the gradually changing network of an individual but complex in the other cases. In particular, the CSD trajectories from baseline to follow-up varied between individuals, and it is not trivial to generalize the time courses of CSD changes specific to groups. The four examples in Fig. 11 do not represent all the diversity of each group but suggest the importance of individual-level computational modeling and simulation.

7.2. Core parameters for CSD progression

If the progress of a model parameter continues along the direction from baseline to follow-up, how will the CSD progress in the SI-H group? Which parameters are more influential in inducing progressive CSD changes from follow-up?

Regarding these questions, we used a virtual perturbation analysis of all model parameters in DMN and AHN. We explored the core parameters that influence the CSD progression of each patient in the SI-H group. For all parameters, we individually altered the follow-up parameter to progress 50% in the direction from baseline to follow-up. If a follow-up parameter was increased from baseline, we added the parameter with $\log(1.5)$, which was driven by considering a real biological effect, i.e., $0.5X_0 \exp(x)$. If a follow-up parameter is smaller than the baseline, we subtracted $\log(1.5)$ from the follow-up parameter. To evaluate the influence of a parameter p on the progression of CSD, we perturbed the follow-up system with a set of parameters $\tilde{\Theta}^{(p)}$, defined as follows.

$$\tilde{\Theta}^{(p)} = \left\{ \Theta_p^{(2)}, \Theta_p^{(2)} + \log(1.5) \cdot \text{sign}(\Theta_p^{(2)} - \Theta_p^{(1)}) \right\} \quad (24)$$

Here, $\text{sign}(\Theta^{(2)} - \Theta^{(1)})$ represents the sign of $(\Theta_p^{(2)} - \Theta_p^{(1)})$, i.e., 1 for $\Theta^{(2)} - \Theta^{(1)} > 0$, -1 for $\Theta^{(2)} - \Theta^{(1)} < 0$.

To measure the influence of each parameter p on the progression of CSD in each patient after follow-up, we used $RMSE_p$, which is defined by the root mean square error between the CSD of the progressive system ($C\tilde{S}D(e, f | \tilde{\Theta}^{(p)})$) and that of follow-up ($CSD^{(2)}(e, f)$) at all $n(E)$ edges and $n(F)$ frequency bands as below.

$$RMSE_p = \sqrt{\frac{1}{n(E) \times n(F)} \sum_{e \in E} \sum_{f \in F} \{C\tilde{S}D(e, f | \tilde{\Theta}^{(p)}) - CSD^{(2)}(e, f)\}^2}. \quad (25)$$

We sorted $RMSE_p$ of all parameters and chose the eight highest core parameters for each individual of the eight patients in the SI-H group. We then counted the number of occurrences of each parameter in the eight patients. Figure 12A and B display $RMSE_p$ and the occurrence counts for each parameter for DMN and AHN.

Despite heterogeneity between individuals, most membrane capacitance parameters ($C^{(i)}$) except d_p , some intrinsic connectivity (γ_{ij}), and

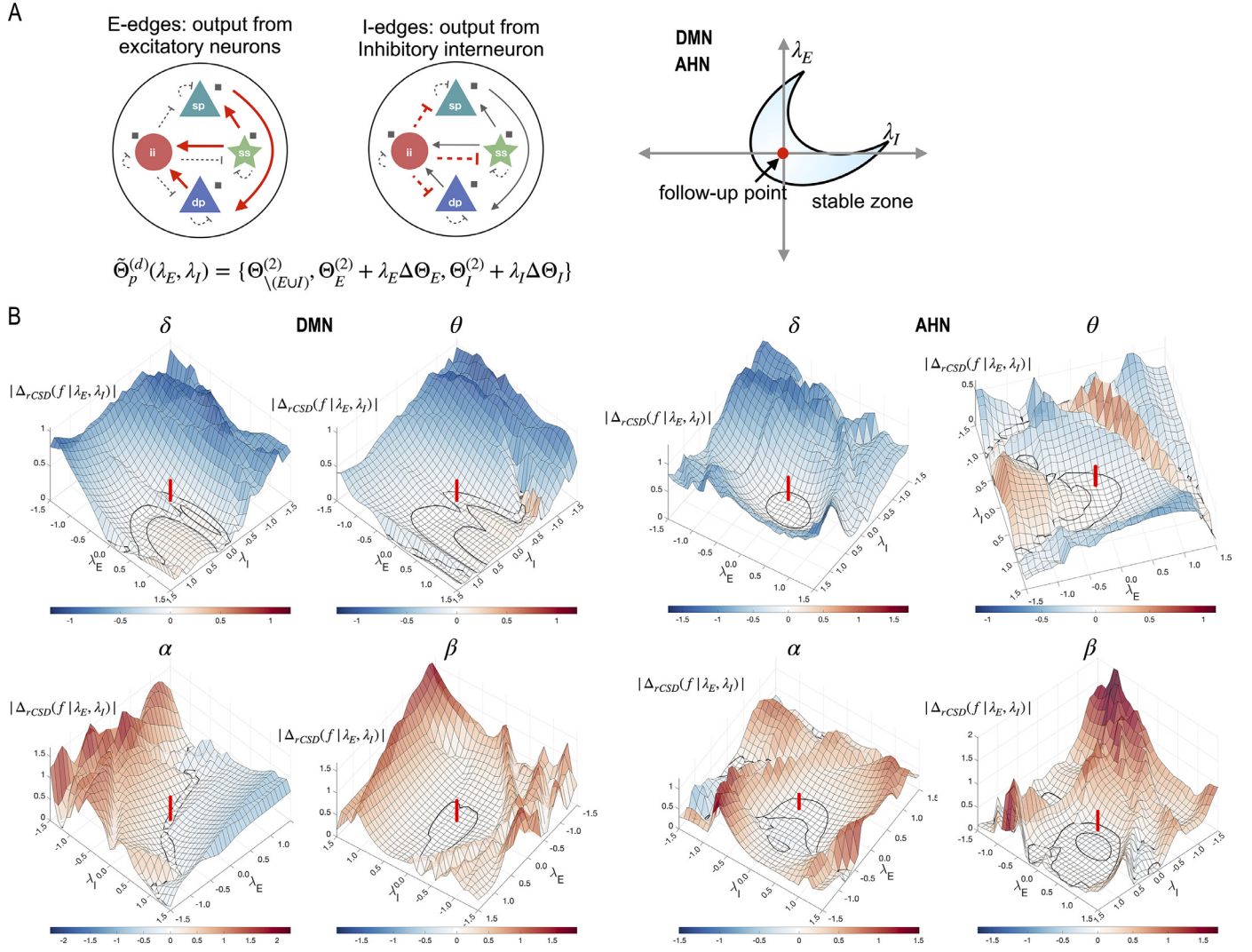


Fig. 10. Effects of excitatory and inhibitory connectivity on CSD frequency shifts. (A) All intrinsic connectivity is divided into two sets: intrinsic connections from an inhibitory subpopulation *ii* to other subpopulations (called I-edges) and all excitatory connections from noninhibitory subpopulations to different subpopulations (E-edges) shown as red arrows. (B) For a diverse pair of excitatory and inhibitory connectivity strengths, the deviation of relative CSD (rCSD) from follow-up CSD (i.e., $\Delta_{rCSD}(f | \lambda_E, \lambda_I)$), a difference between the rCSD simulated with the parameter pair $(\tilde{\Theta}_p^{(d)}(\lambda_E, \lambda_I))$ and that of the follow-up was displayed in color (blue for reduced simulated rCSD and red for increased simulated rCSD compared to follow-up rCSD with its absolute value $(\Delta_{rCSD}(f | \lambda_E, \lambda_I))$ as a landscape amplitude at four frequency bands in DMN and AHN. Black-lined white zones of excitatory and inhibitory connectivity strength indicate where they do not lead to a noticeable deviation of rCSD from the follow-up rCSD (< 0.05). The stable zone surrounds the excitatory and inhibitory connectivity of the follow-up point (red bar) with a different pattern for each frequency band and network. In this stable zone, the excitatory and inhibitory connectivity are interdependent to maintain a similar level of rCSD without deviating from the follow-up rCSD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

time constants of neural dynamics (T_I) in DMN and AHN are the core parameters (Fig. 12C and D).

In DMN, $\gamma_{rLP}(dp \rightarrow dp)$ is influential in six patients and $\gamma_{prCu}(dp \rightarrow dp)$ in four patients. In AHN, $\gamma_{STG}(ii \rightarrow ii)$, $\gamma_{STG}(dp \rightarrow dp)$, and $\gamma_{SMG}(dp \rightarrow dp)$ are detected as cores in five patients.

7.3. Nonlinear interactions effects of parameters on CSD progression

By extending the previous core analysis on the CSD progression, we further investigated the interactions of every pair of parameters using virtual perturbation analysis. The model parameters $\tilde{\Theta}^{(p_1, p_2)}$ of a virtual model with a paired perturbation of (p_1, p_2) , are given by

$$\tilde{\Theta}^{(p_1, p_2)} = \{\Theta_{\setminus\{p_1, p_2\}}^{(2)}, \Theta_{\{p_1, p_2\}}^{(2)} + \log(1.5) \cdot \text{sign}(\Theta_{\{p_1, p_2\}}^{(2)} - \Theta_{\{p_1, p_2\}}^{(1)})\} \quad (26)$$

The effect of interaction between a parameter p_1 and p_2 on the progression of CSD is defined by the root mean square error, $RMSE_{(p_1, p_2)}$ as

below.

$$RMSE_{(p_1, p_2)} = \sqrt{\frac{1}{n(E) \times n(F)} \sum_{e \in E} \sum_{f \in F} \left\{ \widetilde{CSD}(e, f | \tilde{\Theta}^{(p_1, p_2)}) - CSD^{(2)}(e, f) \right\}^2} \quad (27)$$

We defined three types of interactions: 1) positive synergistic interaction, 2) negative synergistic interaction, and 3) mild interaction, by comparing the combined $RMSE_{(p_1, p_2)}$ with separate $RMSE_{p_1}$ and $RMSE_{p_2}$.

$$I(p_1, p_2) = \begin{cases} -1 & \text{for } RMSE_{(p_1, p_2)} < \min(RMSE_{p_1}, RMSE_{p_2}) \\ 0 & \text{for } \min(RMSE_{p_1}, RMSE_{p_2}) \leq RMSE_{(p_1, p_2)} < (RMSE_{p_1} + RMSE_{p_2}) \\ 1 & \text{for } RMSE_{(p_1, p_2)} \geq (RMSE_{p_1} + RMSE_{p_2}) \end{cases} \quad (28)$$

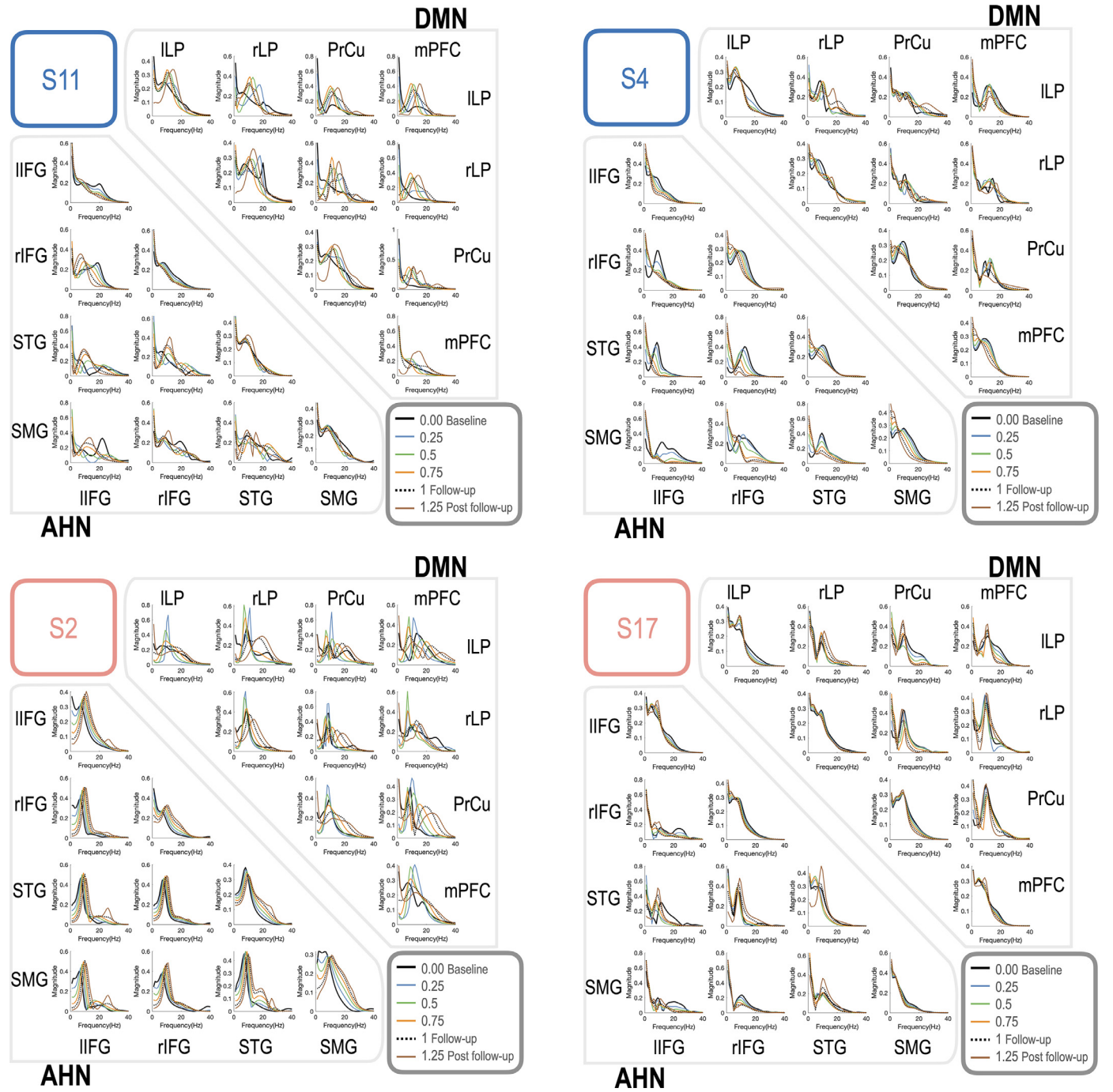


Fig. 11. CSD evolution trajectory from baseline to follow-up when the model parameters change from baseline to follow-up with ratios of 0.25, 0.5, 0.75, 1.0, and 1.25. $\lambda = 0$ and $\lambda = 1$ generate CSDs with parameters of baseline and follow-up. $\lambda = 1.25$ correspond to the future time point with extrapolated parameters after follow-up. The CSD trajectory of DMN and AHN are shown for two patients, S11 and S4 in SI-L group and S2 and S17 in SI-H group.

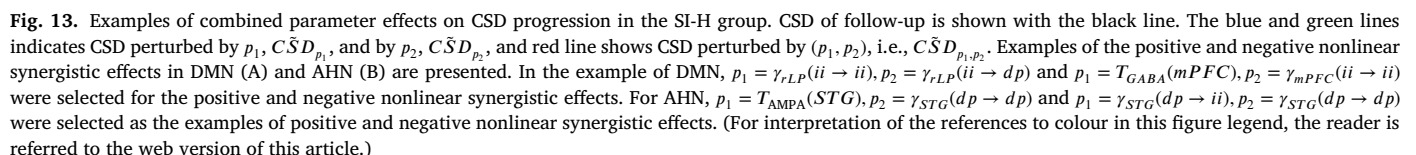
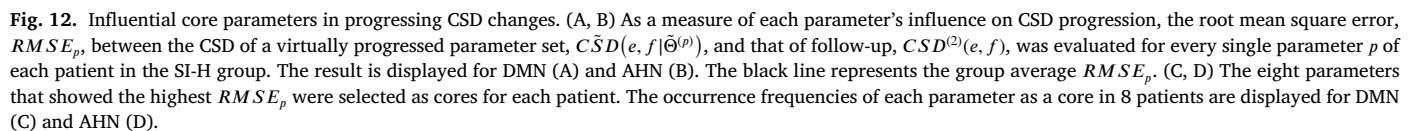
Here, the mild interaction indicates interactions between positive and negative synergistic interactions, including an additive linear interaction and most of the negative but mild synergistic interactions. For each patient in the SI-H group, we evaluated $I(p_1, p_2)$ for all pairs of p_1 and p_2 in the best model. This leads to an interaction map among parameters. We then averaged individuals' interaction maps for display.

Figure 13 illustrates examples of positive and negative synergistic interactions in DMN and AHN. In the example of positive synergistic interaction in DMN, perturbations of $p_1 = \gamma_{rLP}(ii \rightarrow ii)$, $p_2 = \gamma_{rLP}(ii \rightarrow dp)$ separately do not cause significant progressions in CSD after follow-up. When perturbed together, the progression of the CSD from follow-up is

higher than the sum of each progression. This nonlinear interaction is found similarly in AHN, between $p_1 = T_{AMPA}(STG)$, $p_2 = \gamma_{STG}(dp \rightarrow dp)$.

In the negative synergistic interaction examples in DMN and AHN, individual perturbations of $p_1 = T_{GABA}(mPFC)$, $p_2 = \gamma_{mPFC}(ii \rightarrow ii)$ in DMN and $p_1 = \gamma_{STG}(dp \rightarrow ii)$, $p_2 = \gamma_{STG}(dp \rightarrow dp)$ in AHN show the progression of CSD from follow-up, but combined perturbation reduces the progression, lower than the minimal progression, by separate perturbation of the two parameters, canceling separate perturbation effects.

Figure 14 and Table 5 summarize the results of the nonlinear interaction analysis of all pairs of parameters. The average interaction map of the group in Fig. 14 reveals the most positive or negative non-



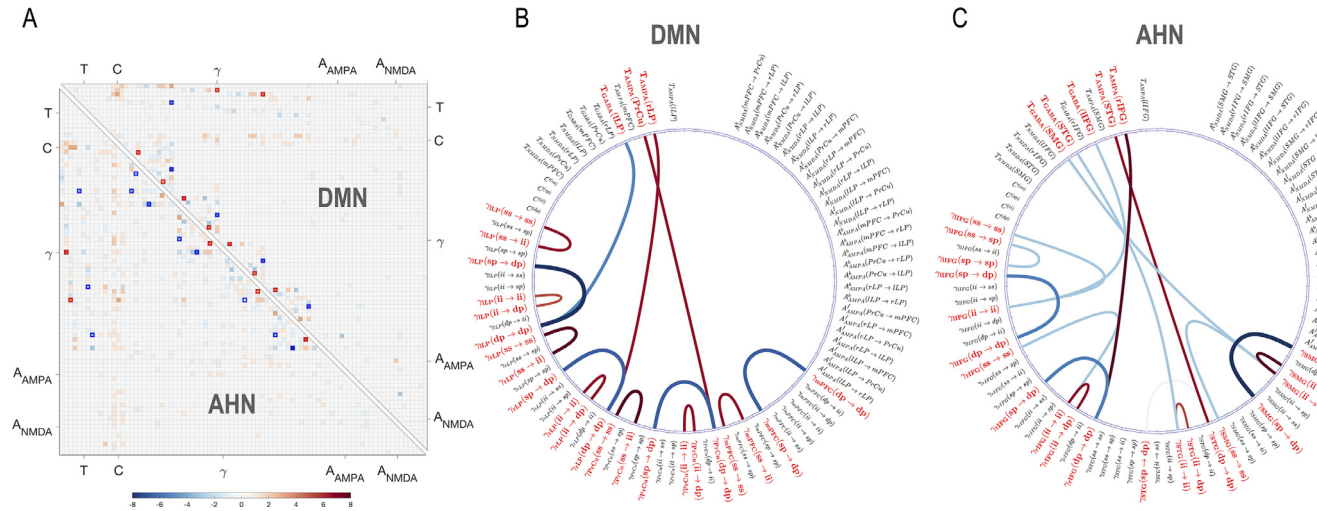


Fig. 14. The group average interaction maps of DMN and AHN. The group interaction maps comprised the interaction effect on the CSD progression from follow-up between all pairs of model parameters in the SI-H group after combined parameter perturbation. The group average interaction maps are illustrated as adjacency matrices (including all parameter pairs) and circular graphs (parameter pairs of nonlinear interactions in more than 4 out of 8 patients) for DMN and AHN. The positive and negative nonlinear synergistic interactions are colored in red and blue in the circular maps. Most positive or negative nonlinear interactions were found between the intrinsic connectivity (γ_k) in a region. Nonlinear interactions are also found between some time constants and intrinsic connectivity in a region. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5

Parameter pairs of synergistic interactions on CSD progression.

DMN		AHN	
Positive synergistic interactions	Patients	Positive synergistic interactions	Patients
$T_{AMPA}(rLP) \leftrightarrow \gamma_{rLP}(dp \rightarrow dp)$	4	$T_{AMPA}(rIFG) \leftrightarrow \gamma_{rIFG}(dp \rightarrow dp)$	5
$T_{AMPA}(PrCu) \leftrightarrow \gamma_{PrCu}(dp \rightarrow dp)$	4	$T_{AMPA}(STG) \leftrightarrow \gamma_{STG}(dp \rightarrow dp)$	4
$\gamma_{ILP}(ss \rightarrow ss) \leftrightarrow \gamma_{ILP}(ss \rightarrow ii)$	4	$\gamma_{rIFG}(ii \rightarrow ii) \leftrightarrow \gamma_{rIFG}(ii \rightarrow dp)$	4
$\gamma_{rLP}(ss \rightarrow ss) \leftrightarrow \gamma_{rLP}(ss \rightarrow ii)$	5	$\gamma_{STG}(ii \rightarrow ii) \leftrightarrow \gamma_{STG}(ii \rightarrow dp)$	4
$\gamma_{PrCu}(ss \rightarrow ss) \leftrightarrow \gamma_{PrCu}(ss \rightarrow ii)$	5	$\gamma_{SMG}(ii \rightarrow ii) \leftrightarrow \gamma_{SMG}(ii \rightarrow dp)$	5
$\gamma_{mPFC}(ss \rightarrow ss) \leftrightarrow \gamma_{mPFC}(ss \rightarrow ii)$	4		
$\gamma_{ILP}(ii \rightarrow ii) \leftrightarrow \gamma_{ILP}(ii \rightarrow dp)$	4	Negative synergistic interactions	Patients
$\gamma_{rLP}(ii \rightarrow ii) \leftrightarrow \gamma_{rLP}(ii \rightarrow dp)$	4	$T_{GABA}(lIFG) \leftrightarrow \gamma_{lIFG}(ii \rightarrow ii)$	4
$\gamma_{PrCu}(ii \rightarrow ii) \leftrightarrow \gamma_{PrCu}(ii \rightarrow dp)$	4	$T_{GABA}(STG) \leftrightarrow \gamma_{STG}(ii \rightarrow ii)$	4
Negative synergistic interactions	Patients	$T_{GABA}(SMG) \leftrightarrow \gamma_{SMG}(ii \rightarrow ii)$	4
$T_{GABA}(lLP) \leftrightarrow \gamma_{lLP}(dp \rightarrow dp)$	5	$\gamma_{lIFG}(sp \rightarrow dp) \leftrightarrow \gamma_{lIFG}(dp \rightarrow dp)$	6
$\gamma_{lLP}(sp \rightarrow dp) \leftrightarrow \gamma_{lLP}(dp \rightarrow dp)$	7	$\gamma_{rIFG}(sp \rightarrow dp) \leftrightarrow \gamma_{rIFG}(dp \rightarrow dp)$	6
$\gamma_{rLP}(sp \rightarrow dp) \leftrightarrow \gamma_{rLP}(dp \rightarrow dp)$	7	$\gamma_{STG}(sp \rightarrow dp) \leftrightarrow \gamma_{STG}(dp \rightarrow dp)$	4
$\gamma_{PrCu}(sp \rightarrow dp) \leftrightarrow \gamma_{PrCu}(dp \rightarrow dp)$	6	$\gamma_{SMG}(sp \rightarrow dp) \leftrightarrow \gamma_{SMG}(dp \rightarrow dp)$	8
$\gamma_{mPFC}(sp \rightarrow dp) \leftrightarrow \gamma_{mPFC}(dp \rightarrow dp)$	6	$\gamma_{lIFG}(ss \rightarrow ss) \leftrightarrow \gamma_{lIFG}(ii \rightarrow ii)$	4
		$\gamma_{rIFG}(ss \rightarrow ss) \leftrightarrow \gamma_{rIFG}(ii \rightarrow ii)$	4
		$\gamma_{SMG}(ss \rightarrow ss) \leftrightarrow \gamma_{SMG}(ii \rightarrow ii)$	4
		$\gamma_{lIFG}(ss \rightarrow sp) \leftrightarrow \gamma_{lIFG}(sp \rightarrow sp)$	4

linear interactions between intrinsic connectivity (γ_k) in the same region. Nonlinear interactions are also found between some time constants and intrinsic connectivity in the same region. For example, combinations of two intrinsic connectivities such as $\gamma(sp \rightarrow dp) \leftrightarrow \gamma(dp \rightarrow dp)$, $\gamma(ss \rightarrow ss) \leftrightarrow \gamma(ii \rightarrow ii)$, $\gamma(ii \rightarrow ss) \leftrightarrow \gamma(ii \rightarrow ii)$, and $\gamma(ss \rightarrow sp) \leftrightarrow \gamma(sp \rightarrow sp)$ show negative synergistic interactions. T_{GABA} and $\gamma(ii \rightarrow ii)$ or T_{GABA} and $\gamma(dp \rightarrow dp)$ also show a negative synergistic interaction.

On the other hand, combinations of the AMPA time constant (T_{AMPA}) and the intrinsic self-connection of $dp - dp$ ($\gamma(dp \rightarrow dp)$) or combinations of $\gamma(ii \rightarrow ii)$ and $\gamma(ii \rightarrow dp)$ in the same region induce positive synergistic interactions in both networks. The interactions between $\gamma(ss \rightarrow ss)$ and $\gamma_{PrCu}(ss \rightarrow ii)$ are positive synergistic only in DMN.

8. Discussion

In the present study, we explored long-term changes in neurobiological properties at hierarchical levels of the CMM-NMDA model at DMN

and AHN in clozapine-treated patients with schizophrenia. We identified neurobiological properties at three hierarchical levels (cellular-level neural properties, intrinsic connectivity, and extrinsic connectivity) associated with medication duration and symptomatic improvement in schizophrenia. To evaluate the precise effects of each neurobiological property on the EEG CSD, we performed virtual perturbation analyses, taking advantage of the generative nature of the computational model. Virtual perturbation analysis includes a method to evaluate nonlinear interactions between pairs of neurobiological properties that affect CSDs.

Our results suggested that: a) longitudinal changes occur in neurobiological properties across hierarchical levels; b) changes associated with medication duration and symptomatic improvement are dominant in intrinsic connectivity; c) each neurobiological property plays a specific role in the frequency shift of EEG CSD; d) both inhibitory and excitatory connectivity complement CSD alteration; and e) nonlinear synergistic interactions between neural properties contribute to CSD progression after follow-up.

8.1. Multiscale neuropharmacological modeling with the CMM-NMDA

Computational modeling involves growing attention to bridge the microscale (channel level), mesoscale (intra-regional level), and macroscale (inter-regional level) interactions in the neurobiological hierarchy. An increasing number of computational modeling studies have been conducted in neuropharmacology. Among computational models for neuropharmacology, the CMM-NMDA receives increasing attention because of its multiscale modeling capability of neurobiological circuits.

Moran et al. (2013b) applied the CMM-NMDA model to analyze the EEG signals obtained during oddball experiments. The model helped clarify the roles of the neuromodulator, acetylcholine, in perception and learning under uncertainty. Symmonds et al. (2018) analyzed resting state EEG data to investigate the receptor function of patients with NMDA receptor antibody encephalitis. The CMM-NMDA models have been further extended to solve various problems. A separate study (Adams et al., 2020) explored the role of the tiagabine GABA reuptake inhibitor in the oddball auditory task using an extended CMM with six neural populations for a local circuit for MEG data. Another study (Shaw et al., 2020) introduced a thalamocortical model with neural populations from four cortical regions. They studied the effects of ketamine on task-induced cortical oscillations, including increases in high-frequency oscillations (gamma band) and decreases in low-frequency oscillations (theta and alpha bands).

In line with these neuropharmacological modeling studies, we chose a CMM-NMDA model to explore long-term neurobiological changes in clozapine-treated patients, taking advantage of its multiscale model characteristics. Patients with schizophrenia treated with clozapine were resistant to drugs other than clozapine. Unlike variations in drug types and doses during early treatment, these patients received similar dose levels between patients without significant dose changes. Consequently, patients treated with clozapine with schizophrenia are advantageous for computational modeling to explore the long-term effects of clozapine on schizophrenia due to the reduced confounder effects of the type, dose, and changes in medication.

To apply the CMM-NMDA model to longitudinal EEG in patients with schizophrenia treated with clozapine, we focused on DMN and AHN based on previous studies (Andreasen and Flaum, 1991; Galindo et al., 2018; Garrity et al., 2007; Li et al., 2017; Sambataro et al., 2010; Stephane et al., 2001; Swanson et al., 2011). As a Bayesian approach, the best models for DMN and AHN (Fig. 4) in the resting state were chosen by performing a BMR and BMS analysis (Friston and Penny, 2011; Friston et al., 2016; Zeidman et al., 2019). To constrain the search space of the model within biological plausibility, we initially constructed the topology of the model with neurobiologically known connectivity and allowed other edges previously unexplored or unreported to be searched. This guided search of the network topology is necessary, as the best model chosen by the free energy criterion may not necessarily be the human brain system.

The hierarchy of the best DMN model was in the order of mPFC > PrCu > LP with a direct connection from the LP to the mPFC (Fig. 4A), which is consistent with a previous EEG DCM study (Steen et al., 2019). For the AHN model, we set the basic hierarchy of the left hemisphere to IFG ← SMG ← STG according to Jardri et al. (2011). In the best model of AHN, rIFG appears to be hierarchically lower than lIFG but higher than the SMG and the STG (Fig. 4B). This circuit topology is partly evidenced by a language processing study in which the lIFG plays an integrative role and the rIFG supports the lIFG by providing specific information (Steines et al., 2021).

8.2. Strategy for exploring long-term evolvement of neurobiological properties

In the neurobiological hierarchy, it is reasonable to consider the effects of clozapine treatment hierarchically. The cellular or channel-level properties, the initial target of clozapine, may induce changes in intrinsic

and extrinsic interregional connectivity due to plasticity at different temporal scales. However, how one-level change affects others requires a more complex hierarchical and long-term chronometric model, which remains an important topic for future study. Instead of exploring the propagation of drug effect across hierarchical levels, we used a CMM-NMDA model that includes all hierarchical level neural parameters in a model. To mitigate limitations in studying the evolution of interactions across hierarchical levels, we have tried to identify hierarchical-level-specific effects on EEG CSD. We also explored nonlinear interactions between model parameters within and through hierarchical levels. Despite being simplified and thus blind to temporal orders, we expected more notable changes in intrinsic connectivity within a local region than in extrinsic interregional connectivity due to the neuropharmacological mechanism of antipsychotic drugs.

We also lack a generative model from neurobiological properties to psychotic symptoms, which are hierarchically beyond the EEG level, the link of which is a fundamental question of human brain research. Instead of exploring the causal relationship between neurobiological properties and symptoms, we remain at the correlative link, employing the hierarchical Bayesian framework. We specified the neurobiological changes at each level according to the medication duration and symptomatic improvement in the form of a group design matrix in the PEB analysis.

Since medication duration and symptom improvement ratio were centered on the mean, the common effect represents an average longitudinal difference in the neurobiological model parameter under a group-average duration of the medication (between follow-up and baseline) with a group-average symptom improvement ratio. Meanwhile, the effects of treatment duration and improvement ratio are patient-specific. In the current study with patients resistant to other drugs, relatively stabilized in clozapine dose, a high correlation exists between symptomatic improvement ratios and medication durations. In this sense, the effect of the improvement ratio is attributable to the individual characteristics that respond to clozapine, unexplained by the duration of clozapine treatment.

8.3. Neurobiological properties related to medication duration and symptom improvement

Clozapine, a selective monoaminergic antagonist, shows a high affinity for serotonin type 2 (5HT₂), adrenergic type 1 dopamine D₄ receptors, and histaminergic receptors H₁ (Nucifora et al., 2017). Clozapine also acts as an antagonist of other receptors, but with lower affinity. As these receptors are mainly distributed in the serotonin and dopamine circuits, which overlap with DMN (Conio et al., 2020), the effects of clozapine can be directly associated with the DMN regions but indirectly with AHN.

Longitudinal neurobiological changes associated with medication duration and symptom improvement occur across hierarchical levels in patients with clozapine, primarily in intrinsic connectivity (Fig. 7). Extrinsic connectivity changes were found predominantly in the common effect, showing that the extrinsic connection decreases along the acquisition time points.

In DMN, the longitudinal decrease in the extrinsic connection was commonly found in the forward and backward interhemispheric AMPA connection between the bilateral parietal lobe (*lLP* → *rLP*). The *rLP* and mPFC are dominant regions that show changes in intrinsic connectivity associated with the symptom improvement (Fig. 7A). In mPFC, the connectivity of the superior pyramidal cell (*sp*) to the deep pyramidal cell (*dp*) is generally reduced at follow-up (common effect), and the decrease was also negatively associated with symptom improvement. In other words, this decrease was severe in patients who displayed more remarkable improvement (Fig. 7B and Table 3). The greater increase in intrinsic connectivity from deep pyramidal cells (*dp*) to inhibitory interneurons (*ii*) of the mPFC was also found in the more improved patients.

Regarding the effects related to symptom improvement, increased connectivity from the inhibitory neural population (*ii*) to the spiny stellate population (*ss*) (*ii* → *ss*) in ILP and rLP of DMN (Fig. 7A and Table 3) implies that recovery of the inhibitory GABAergic connection may be associated with improved symptoms of schizophrenia. In rLP and mPFC, an increase in excitatory connectivity from the deep pyramidal population (*dp*) to the inhibitory population (*ii*) (*dp* → *ii*), which could also increase the activity of the inhibitory neural population (*ii*), was identified as the effect of symptom improvement.

In AHN, the extrinsic connectivity from STG to SMG (STG → SMG) generally decreases in the patient group at follow-up compared to baseline. Meanwhile, an increase in extrinsic connection from STG to IIFG (STG → IIFG) in AHN is associated with the symptomatic improvement ratio (Fig. 7B). Schizophrenia showed reduced thickness and increased metabolism in the IFG and temporal lobe of the left hemisphere (Park et al., 2006). Patients with schizophrenia have reduced diffusion anisotropy in the uncinate fasciculus, a tract that connects the temporal and frontal cortices (Kubicki et al., 2005). A decrease in structural and functional connectivity was found between the left IFG and the temporal lobe compared to the healthy control group (Jeong et al., 2009). If we consider symptomatic improvement as closer to a healthy circuit, the increase in the extrinsic connectivity from STG to IIFG is consistent with higher connectivity in the healthy group compared to the schizophrenia group in previous studies.

The left STG in AHN also shows outstanding changes in intrinsic connectivity in the group average (common effect) and the medication duration effect (Fig. 7B). Among them, the inhibitory neural population (*ii*) was prominent in the intrinsic connectivity of STG.

Clozapine treatment affects not only intrinsic and extrinsic connectivity but also cellular-level properties, such as membrane capacitance and NMDA time constants. In particular, membrane capacitance in the deep pyramidal population (*dp*) of all regions of DMN was negatively associated with the symptom improvement ratio (Fig. 7B and Table 3). Membrane capacitance is reported to influence synaptic efficacy and determine the speed of signal propagation along dendrites and unmyelinated axons (Gentet et al., 2000). Changes in NMDA time constants in the parietal lobe were found to be positively associated with medication duration, indicating the slowdown of the NMDA receptor response for longer medication durations.

8.4. Relationship between CSD changes and neurobiological changes

Previous studies using EEG power spectral analysis have reported EEG alterations in patients treated with clozapine with schizophrenia. Most studies reported clozapine-induced increased slow wave (delta, theta) (Adams et al., 2022; Hyun et al., 2011; Jackson and Seneviratne, 2019; Knott et al., 2001; Ozaki et al., 2021; Raymond et al., 2022). However, how receptor-level clozapine affects EEG signals and symptom improvement in patients with schizophrenia is not well understood. In contrast to the previous power spectral analysis method, we evaluated the cross-spectra changes at the source level, which reflect changes in interregional communications among brain regions. Due to considerable methodological differences compared to previous studies (e.g., analysis at EEG sensor level versus source level, power spectrum without interaction information between brain regions versus CSD with inter-regional interaction information, CSD without and with total power normalization for global power changes versus edge-specific frequency shifts), the current CSD results cannot be directly compared with previous results analyzed using power spectrum at the channel level without normalization.

During clozapine treatment, frequency-dependent relative CSDs in DMN generally show decreased or negative directional longitudinal changes in slow oscillations (delta or theta frequency bands) but increase in the higher frequency oscillations (alpha or beta frequency bands) on average across group patients (Fig. 6C).

In DMN, SI-related changes were found in the beta frequency channel, with more increase in interhemispheric connectivity between ILP and rLP, but reduced power spectral changes in mPFC and rLP in more improved patients (Fig. 6C). In AHN, more reduction was found in theta frequency CSD powers across the hemispheres and the autopower spectra of STG and IIFG (Fig. 6D) in the more improved patients.

Of note, the relationship between changes in CSD power in the GLM analysis and changes in the CMM-NMDA parameter in the PEB analysis is not straightforward. There was no apparent correspondence between the edges of the CSD and extrinsic connectivity associated with the common, medication durations, and symptom improvements. The lack of correspondence suggests that the change in CSD power at a specific edge is not simply the result of extrinsic connectivity corresponding to the edge but may be an interaction of intrinsic connectivity. Consistent with this interpretation, Gao et al. (2022) suggests that GABA deficiency may result in abnormal local circuitry and, thus, long-distance connectivity between several brain regions, including the dopamine system. In our analysis and simulation, the changes in CSD were mainly driven by interactions between intrinsic connectivity rather than extrinsic connectivity between regions. Because interregional connectivity is regulated by supra pyramidal cells (*sp*) for forward connections and deep pyramidal cells (*dp*) for backward connections (see Fig. 3), the activity of these regions may explain the changes in interregional CSD. Since the system is interwoven, it may not be easy to differentiate specific effects from the whole in explaining the longitudinal changes of the CSD. However, these results imply the need to explore neural-level analysis to better understand changes in CSD.

8.5. Virtual perturbation analyses

To explore the role of neurobiological properties in longitudinal EEG changes in patients with clozapine, we took advantage of computational modeling to generate signals with different parameters, that is, virtual perturbation (Figs. 8–14). The virtual perturbation analysis effectively expands our understanding of the target system by artificially changing the model parameters. In Fig. 8, we were able to identify the sensitivity of each neurobiological property to the frequency shift of CSD from baseline to follow-up. Virtual perturbation analysis also reveals the contribution of each neural parameter set to the follow-up EEG, as shown in Fig. 9. We found that intrinsic neural properties and intrinsic connectivity are differentially influential in the formation of follow-up EEG CSD by affecting different frequency bands.

The sensitivity of each neurobiological property and the contribution of each neural parameter set based on Eqs. (19) and (20) are conceptually similar but have slightly different indications. The first is to perturb the baseline system by replacing a baseline parameter with that of the follow-up. In contrast, the second is to perturb the follow-up system by replacing a parameter or a set of parameters of follow-up with that (or those) of the baseline. As many parameters should be involved together to achieve follow-up CSD, the effect of a single parameter alone in the baseline system without considering other parameters may not adequately represent the role of each parameter on CSD change toward the follow-up. In contrast, the follow-up system can be regarded as a result of changes in all parameters and all interactions between the parameters during the time courses. The contribution of a parameter was evaluated by the CSD deviation from the follow-up after replacing the parameter with the baseline while keeping all other follow-up parameters. In the current study, we preferred to perturb the follow-up system except for Perturbation 1 in Table 4 (Section 5.1).

Virtual perturbation analysis is also helpful in exploring each individual's CSD trajectory from baseline to follow-up, as shown in Fig. 11. For this simulation, we simplified the transition model by changing the vector of model parameters proportional to the difference in vectors between the follow-up and baseline by ignoring the nonlinear transition. The nonlinear transition, investigated in previous studies for different

purposes (Kang et al., 2021; Park and Kang, 2021), could be further investigated.

We used virtual perturbation analysis to explore the complementary relationship between intrinsic excitatory and inhibitory connectivity, as shown in Fig. 9. In the neurobiological system, the balance between excitation and inhibition is critical for optimal signal generation and transmission. In schizophrenia, dysfunction of the NMDA receptor and GABAergic abnormalities have been proposed to induce excitation/inhibition imbalance (Gao and Penzes, 2015; Jardri and Denève, 2013; O'Donnell, 2011; Yang et al., 2016).

The effects of the excitatory and inhibitory connectivity strengths on relative changes in CSD differed depending on frequency bands and networks. For example, in DMN, the low-frequency band (δ and θ) rCSDs remarkably get close to the pattern of the follow-up system (increased from baseline, colored blue) as the strengths of the excitatory and inhibitory connectivity approach to the follow-up system. They stayed at a similar level without a significant change in generating rCSDs even after a further increase in both connectivities from the follow-up. This pattern was not found in other frequency bands in DMN and AHN, except the alpha band in AHN. The excitatory and inhibitory increase toward the target system of AHN induces a reduction in the rCSDs in the beta frequency band, followed by a stable state after a further rise in connectivity. We found a stable excitatory/inhibitory parameter zone that generates CSD that does not deviate significantly from the follow-up CSD. Any combination of excitatory and inhibitory strength within this stable zone has a CSD similar to that in follow-up. The stable zones are relatively narrow and form a complex shape in some frequency bands, indicating the complementary dependency between excitatory and inhibitory connectivity in these frequency bands. The complementary dependency between excitatory and inhibitory connectivity was crucial in inducing the alpha frequency band rCSD shifts in DMN. In the beta frequency band in DMN, the inhibitory connectivity strength is critical for the rCSD change but is less dependent on the excitatory connectivity strength. The stable zone of the theta band in AHN is relatively similar to that of the alpha band in DMN, located between the increase and decrease of frequency-specific rCSD. This analysis suggests that the complementary characteristic between excitatory and inhibitory connectivity is a common phenomenon regardless of DMN or AHN, despite slightly different shapes depending on the frequency bands and networks. The analysis also informs us of the progression of treatment effects after follow-up. As shown in the delta and theta frequency bands in DMN and the beta frequency band in AHN, further excitatory and inhibitory connectivity changes will not induce significant changes in rCSD in those frequency bands.

8.6. Nonlinear synergistic interactions of parameters for CSD

The CSD time courses simulated from baseline to follow-up in Fig. 11 and the influential cores reflected in $RMSE_p$ in Fig. 12 showed high interindividual variability, suggesting the importance of individualized simulation. Due to the high variability between individuals, we extracted the core parameters for the progression of CSD from follow-up from each individual in the SI-H group and evaluated their frequency of occurrence between individuals. The membrane capacitances of all neural populations except the dp population were identified as influential core parameters in both DMN and AHN. Intrinsic connectivities, $dp \rightarrow dp$ in the LLP of DMN, in the STG and SMG of AHN, and $ii \rightarrow ii$ in the STG of AHN were also core parameters in most patients.

We found that some network systems show highly complex trajectories, as shown in the DMN of Fig. 11. This complexity might be related to the nonlinear interactions between neural parameters. Consequently, we proposed a novel method to generate an interaction map to explore the effects of nonlinear interaction between all pairs of parameters on the progression of the CSD after follow-up.

We only evaluated interactions of two parameters; Exploring interactions of more than two is theoretically possible in the current framework, but it will require a large amount of computation. Similarly to

the current interaction analysis in Eq. (14), the parameter interaction analysis can be applied in various ways. Indeed, we applied the interaction analysis of the follow-up parameters in achieving the follow-up CSD at different frequency bands, which was presented in the Supplementary Section “Nonlinear interaction effects of parameters in inducing frequency-specific follow-up rCSDs”. It is also possible to evaluate the nonlinear interactions of all pairs of parameters in the path from baseline to follow-up. Notably, perturbation of a system by replacing a follow-up parameter with that of the baseline or a baseline parameter with that of the follow-up has a limitation when the parameters of the baseline and follow-up do not sufficiently differ; clozapine treatment might not successfully alter the parameter from the baseline despite its importance in cure. In this case, the replacement of parameters may not induce a sufficient change in CSD and cause a minimal interaction effect with other parameters. Therefore, instead of using the difference between follow-up and baseline, we evaluated a continuation effect of treatment after follow-up by altering all parameters with a 150% increase or decrease according to the time course from baseline to follow-up.

We found nonlinear interactions among parameters. We classified them into positive and negative synergistic interactions and mild interactions between the two. In the negative synergistic interaction, individual perturbations induce CSD progressions from follow-up, but the combined perturbation significantly reduces progression from follow-up, canceling separate perturbation effects.

According to the group-averaged interaction map (Fig. 14), most positive or negative nonlinear interactions were found when the intrinsic connectivity of the same region (γ_k) was perturbed together. Nonlinear interactions were also found between some time constants and intrinsic connectivity in a region.

The existence of nonlinear interactions highlights the complex and interconnected nature of the neural system. The finding that negative synergistic effects were more prevalent than positive synergistic effects is noteworthy. Negative synergistic interaction may be associated with maintaining homeostasis in the biological system for its stability and proper functioning. For example, in the regulation of metabolic pathways, negative synergistic effects between enzymes can prevent the accumulation of harmful by-products and maintain the appropriate balance of metabolic intermediates (Cruchaga et al., 2005; García-Fuente et al., 2018; Lai et al., 2003). Similarly, in the regulation of gene expression, negative synergistic effects between transcription factors can prevent gene overexpression and maintain cell homeostasis (Patterson et al., 2021).

On the other hand, positive synergistic interactions can result in increased activity or production of some biomolecules. For example, when regulating gene expression, positive synergistic effects between transcription factors can result in increased expression of genes involved in critical cellular processes, such as cell growth and differentiation (Ramanathan et al., 2007). Similarly, in the regulation of metabolic pathways, positive synergistic effects between enzymes or biochemical regulators can result in increased production of some biomolecules, such as neurotransmitters or hormones (Papa et al., 2022; Roell et al., 2017).

Similar synergistic effects have been reported in biological system control problems (García-Fuente et al., 2018; Meyer et al., 2019; Narayan et al., 2020; Roell et al., 2017; 2017; Sagar et al., 2017; Sinzger et al., 2019; Wooten et al., 2021; Yin et al., 2014; Zhang et al., 2017), emphasizing the importance of considering the combined effects of multiple regulators in these systems. The presence of nonlinear synergistic interaction in a brain system makes the prediction and control of the system's response to perturbations complex (Kang et al., 2021; Park and Kang, 2021). More research is needed to understand the underlying mechanisms of nonlinear interactions and their impact on the neural system. However, current virtual perturbation analysis gives some intuition and provides a framework to explore how the system will change for continuous treatment or a new treatment targeting some pairs of neural parameters. Indeed, the nonlinear interaction of parameters was

evaluated with respect to the progression of CSD from follow-up, which is an example of prediction after a specific treatment. This scheme could be used for optimal treatment planning.

8.7. Limitations and future research direction

The study has several limitations. First, we analyzed the long-term longitudinal EEG data obtained from a limited number of patients. Taking into account individual variations in treatment responses or the etiology of schizophrenia in each patient, a larger patient dataset could be crucial for a more solid conclusion. We found very heterogeneous EEG changes in patients treated with a single type of clozapine without significant dose changes, which is consistently reported in the previous literature (Ozaki et al., 2021; Risby et al., 1995). The alteration paths of neurobiological properties along the time course would also be heterogeneous between patients, as exemplified in Fig. 11. Thus, generalizing long-term changes in EEG CSD and neurobiological properties among clozapine-treated patients with schizophrenia is not trivial. Considerable data accumulation would greatly help subclassify individuals with respect to EEG CSD and their underlying neurobiological parameters. It should be noted that the reliability of the current results should be considered on two different levels, as the present analysis is made up of individual- and group-level models. Individual-level modeling estimates many model parameters to fit the EEG of each patient. The number of patients in the case of high inter-individual variability will be a more crucial issue in the group-level analysis than in the individual-level parameter estimation. The group-level model in PEB we used is determined by a design matrix explaining individual variations. In this study, we assumed that medication duration and symptomatic improvements are the main factors explaining the inter-individual variation of DCM parameters in patients with schizophrenia. If the linear model with the present factors explains well individual variations of parameters, the model's reliability will primarily depend on subject size. Then more patients will be advantageous in finding reliable parameters for the group-level design matrix. If this group-level linear model is insufficient for explaining the parameter variations, more data itself is insufficient. Therefore, it should be further researched to find the correct group-level model with appropriate variables to explain individual variations.

Second, longitudinal EEG data from drug-naïve patients and patients taking different antipsychotic drugs would help understand clozapine-specific changes in CSD and neurobiological parameters.

Third, validating the CMM-NMDA model for longitudinal EEGs in patients with schizophrenia and virtual perturbation analysis requires further study with empirical data on clozapine treatment. Validation includes electrophysiological studies of animals treated with clozapine. Although the validation of the current model in humans is not straightforward, longitudinal EEG with more time points would help to evaluate and update the current model.

Finally, as mentioned in the previous section, the longitudinal transition of neural circuits is modeled linearly with respect to symptomatic improvements and medication durations. This is too simplistic, and we need a more biological model for long-term network evolution. We also need a biological model for the trans-hierarchical progression of the clozapine effects rather than the current all-in-one model using the CMM-NMDA.

Despite these limitations, the current study provides a method for exploring long-term changes in multiscale neurobiological properties and EEG due to neuropharmacological intervention, currently in the case of clozapine for schizophrenia treatment. This study also provides a framework for using a computational model to specify the role of each neural property and the interactions between neural properties on EEG CSD, which is critical to understanding the long-term mechanism of antipsychotic drugs in psychiatric diseases. Although preliminary and theoretical, the current study is a step toward computational neuropharmacology linking neural circuits with electrophysiological observations in routine clinical practice. The current modeling framework could be fur-

ther extended to investigate the neurobiological mechanisms underlying various treatments for schizophrenia, such as electroconvulsive therapy (ECT), transcranial electrical stimulation (tES), and other psychotropic drugs.

In conclusion, the current study shows how computational modeling can help explore the multiscale link between neuropharmacology and clinical EEG in psychiatric diseases by employing various system analysis methods, which is essential in clinical treatment decisions.

Declaration of Competing Interest

None.

Credit authorship contribution statement

Jinseok Eo: Methodology, Data curation, Software, Writing – original draft. **Jiyoung Kang:** Software, Validation, Writing – original draft. **Tak Youn:** Data curation, Writing – review & editing. **Hae-Jeong Park:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition.

Data availability

Preprocessed EEG of SI-H group data are available at figshare(<https://dx.doi.org/10.6084/m9.figshare.22096418>). An exemplary code for DCM perturbation analysis is available at the github. (<https://github.com/monet-yonseil/rseeg-schizophrenia-clozapine>).

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at [10.1016/j.neuroimage.2023.120161](https://doi.org/10.1016/j.neuroimage.2023.120161).

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