Supplementary Material

Frontostriatothalamic effective connectivity and dopaminergic function in the psychosis continuum

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Appendix. Supplementary Methods and Materials

Table S1. Summary of Connections Associated with Severity of Negative Symptoms in FEP ($n = 46$), FEP-SCZ ($n = 17$), and SCZ ($n = 26$) Patients

Figure S1. Parcellation of Dorsal and Ventral Striatal Regions of Interest in PET Quantification Presented on the MNI 2mm Template

Figure S2. Associations Between Severity of Negative Symptomatology and Effective Connectivity Parameters Across All Cohorts
Appendix. Supplementary Methods and Materials

Participant exclusion criteria

**FEP.** The initial sample size for this group was 61 patients and 27 controls. We excluded 5 patients with poor imaging data, 1 patient with high motion, 3 patients with DCM explaining <75% of the signal variance, and 6 patients with substance induced psychosis. This brought the final sample of patients included in the study to 46. A total of 17 FEP patients had a diagnosis of schizophrenia spectrum disorder (8 schizophrenia, 8 schizophreniform disorder and 1 schizoaffective disorders), making up a subset of FEP-SCZ patients. Other FEP patients were diagnosed with delusional disorder (n = 5), major depressive disorder with psychotic features (n = 10), psychotic disorder not otherwise specified (n = 13), and 1 patient had a missing diagnosis. For the control group, we excluded 3 individuals with high motion (criteria outlined below), and 1 with DCM explaining <75% of the signal variance, resulting in a final sample of 23.

**Established schizophrenia (SCZ).** We excluded 1 patient with poor imaging data, 9 patients with high motion, and 5 with DCM explaining <75% of the signal variance, resulting in a final sample of 36 patients. We excluded 6 controls with high motion and 15 with DCM explaining <75% of the signal variance, resulting in a final sample of 100 controls.

**[^F]DOPA.** Eight individuals did not complete the scanning protocol. We also excluded 3 participants with high motion and 5 participants with DCM explaining <75% of the signal variance. A total of 3 participants had unusable PET scans, bringing the final sample to 33 with both fMRI and PET data.
Spectral dynamic causal modelling

Dynamic causal modelling (DCM) is a Bayesian framework that infers the directed (causal) connectivity among the neuronal systems – referred to as effective connectivity. A DCM for resting state fMRI was proposed based upon a deterministic model that generates predicted cross spectra, referred to as spectral DCM. In order to model resting state activity — in the absence of external stimuli — a stochastic component capturing neural fluctuations is included in the model.

Mathematically, we can express the formulation of the stochastic generative model as a set of two equations. First is the neuronal state equation, namely

\[ \dot{x}(t) = f(x(t), u(t), \theta) + v(t), \quad (S1) \]

and second is the observation equation, which is a static nonlinear mapping from the hidden physiological states in (1) to the observed BOLD activity, and is written as:

\[ y(t) = h(x(t), \varphi) + e(t), \quad (S2) \]

where \( \dot{x}(t) \) is the rate of change of the neuronal states \( x(t) \), \( \theta \) are unknown parameters (i.e., the effective connectivity) and \( v(t) \) (resp. \( e(t) \)) is the stochastic process — called the state noise (resp. the measurement or observation noise) — modelling the random neuronal fluctuations that drive the resting state activity. In the observation equations, \( \varphi \) are the unknown parameters of the (haemodynamic) observation function and \( u(t) \) represents any exogenous (or experimental) inputs that drive the hidden states, which are usually absent in resting-state designs. Spectral DCM furnishes a constrained inversion of the stochastic model by parameterising the neuronal fluctuations \( v(t) \).
Spectral DCM simplifies the generative model by replacing the original timeseries with their second-order statistics (i.e., cross spectra). This means that, instead of estimating time varying hidden states, we are estimating their covariance, which is time invariant. Then we simply need to estimate the covariance of the random fluctuations, where a scale free (power law) form for the state noise (resp. observation noise) is used, motivated from previous work on neuronal activity, as follows:

\[
g_v(\omega, \theta) = \alpha_v \omega^{-\beta_v} \\
g_e(\omega, \theta) = \alpha_e \omega^{-\beta_e}
\]  

(S3)

Here, \( \{\alpha, \beta\} \subset \theta \) are the parameters controlling the amplitudes and exponents of the spectral density of the neural fluctuations. The parameterisation of endogenous fluctuations means that the states are no longer probabilistic; hence the inversion scheme is significantly simpler, requiring estimation of only the parameters (and hyperparameters) of the model.

We used standard Bayesian model inversion to infer the parameters of the model in (1), (2) and (3), from the observed signal \( y(t) \). The description of the Bayesian model inversion procedures based on variational Laplace can be found elsewhere. Parametric Empirical Bayes

Empirical Bayes refers to the Bayesian inversion or fitting of hierarchical models. In hierarchical models, constraints on the posterior density over model parameters at any given level are provided by the level above. These constraints are called empirical priors because they are informed by empirical data. A hierarchical Parametric Empirical Bayes (PEB) model for DCM parameters has recently been introduced, which represents how individual (within-subject) connections derive from the subjects’ group membership. Mathematically, for
DCM studies with $N$ subjects and $M$ parameters per DCM, we have a hierarchical model, where the responses of the $i$-th subject and the distribution of the parameters over subjects can be modeled as:

$$y_i = \Gamma_i^{(1)}(\theta^{(1)}) + \epsilon_i^{(1)}$$

$$\theta^{(1)} = \Gamma^{(2)}(\theta^{(2)}) + \epsilon^{(2)}$$

$$\theta^{(2)} = \eta + \epsilon^{(3)}$$

where, $y_i$ is the BOLD time series from $i$-th subject and $\Gamma_i^{(1)}$ is a nonlinear mapping from the parameters of a model to the predicted response $y$, which in this study was the model in Eq. S1 above. $\epsilon_i^{(1)}$ is independent and identically distributed (i.i.d.) observation noise (equivalent to $e(t)$ in Eq. S2). In this hierarchical form, empirical priors encoding second (between-subject) level effects place constraints on subject-specific parameters. The second level is a linear model where the random effects are parametrised in terms of their precision:

$$\Gamma^{(2)}(\theta^{(2)}) = (X \otimes W)\beta$$

where, $\beta \subset \theta$ are group means or effects encoded by a design matrix with between-subject, $X$, and within-subject, $W$, parts. The between-subject part encodes differences among subjects or covariates such as age, while the within-subject part specifies mixtures of parameters that show random effects. We assume that the first column of the design matrix is a constant term, modelling group means, and subsequent columns encode group differences.
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**Table S1. Summary of Connections Associated with Severity of Negative Symptoms in FEP (n = 46), FEP-SCZ (n = 17), and SCZ (n = 36) Patients**

| Connection | Positive (+) or negative (-) association | Effect size (Hz) | 90% Posterior Confidence Interval (lower bound, upper bound) |
|------------|-----------------------------------------|-----------------|---------------------------------------------------------------|
| **FEP**    |                                         |                 |                                                               |
| dlPFC → dlPFC | +                                      | 0.11            | 0.01, 0.21                                                    |
| Amyg → Thal | -                                       | 0.09            | -0.19, 0.02                                                   |
| Amyg → Hipp | +                                       | 0.08            | 0.02, 0.19                                                   |
| Hipp → Hipp | +                                       | 0.12            | 0.02, 0.22                                                   |
| DC → VTA/SN | -                                       | 0.09            | -0.20, 0.01                                                   |
| VTA/SN → Thal | -                                      | 0.13            | -0.24, -0.03                                                  |
| **FEP-SCZ** |                                         |                 |                                                               |
| vmPFC → Amyg | -                                       | 0.19            | -0.32, -0.05                                                   |
| dlPFC → dlPFC | +                                      | 0.11            | -0.02, 0.24                                                    |
| dlPFC → Thal | +                                       | 0.12            | -0.01, 0.26                                                   |
| dlPFC → DC   | +                                       | 0.09            | -0.06, 0.24                                                   |
| Thal → Amyg  | +                                       | 0.17            | 0.03, 0.30                                                   |
| Amyg → Amyg  | +                                       | 0.14            | 0.00, 0.27                                                   |
| Amyg → Thal  | -                                       | 0.11            | -0.23, 0.02                                                   |
| Hipp → Hipp  | +                                       | 0.14            | 0.01, 0.27                                                   |
| **SCZ**     |                                         |                 |                                                               |
| Thal → Thal  | -                                       | 0.17            | -0.28, -0.06                                                   |
| Thal → vmPFC | +                                       | 0.09            | -0.02, 0.19                                                   |
| Amyg → Amyg | -                                       | 0.16            | -0.27, -0.05                                                   |
| NAcc → NAcc | -                                       | 0.09            | -0.20, 0.03                                                   |
| NAcc → Hipp  | -                                       | 0.10            | -0.22, 0.01                                                   |
| NAcc → VTA/SN | +                                       | 0.11            | -0.01, 0.22                                                   |
| VTA/SN → VTA/SN | +                                    | 0.10            | -0.01, 0.21                                                   |
| VTA/SN → Hipp | -                                       | 0.13            | -0.24, -0.02                                                   |
| VTA/SN → dlPFC | -                                     | 0.11            | -0.22, 0.00                                                   |

FEP: first-episode psychosis group; FEP-SCZ: first-episode psychosis subgroup with a diagnosis of schizophrenia spectrum disorder; SCZ: schizophrenia group.

All connections have the posterior probability (free energy) value of 1.00.

All parameters for between region connections are in Hz. Self-connections are italicized, and values are log-transformed to ensure prior negativity (i.e., inhibitory) constraints on self-connections. A positive value for self-connection denotes increased inhibition, a negative value signifies reduced inhibition.

Negative symptoms measured with BPRS Negative subscale.
Figure S1. Parcellation of Dorsal and Ventral Striatal Regions of Interest in PET Quantification Presented on the MNI 2mm Template. The ventral striatum is in magenta and dorsal striatum is in blue. Striatal ROIs were registered to each person’s anatomical template. PET analysis was restricted to the left hemisphere.
Figure S1. Associations Between Severity of Negative Symptoms and Effective Connectivity Parameters Across All Cohorts. Panels depict associations in (A) FEP (n = 46), (B) FEP-SCZ (n = 17), and (C) SCZ (n = 17). Solid arrows: positive associations between effective connectivity parameters and negative PLEs/symptoms; sashed arrows: negative associations between effective connectivity parameters and negative PLEs/symptoms; gray arrows: associations that were not (significantly) different from the prior. Connections were thresholded at Pp > 0.95.