Intra and inter-individual variability in functional connectomes of patients with First Episode of Psychosis

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ABSTRACT

Patients with Schizophrenia may show different clinical presentations, not only regarding inter-individual comparisons but also in one specific subject over time. In fMRI studies, functional connectomes have been shown to carry valuable individual level information, which can be associated with cognitive and behavioral variables. Moreover, functional connectomes have been used to identify subjects within a group, as if they were fingerprints. For the particular case of Schizophrenia, it has been shown that there is reduced connectome stability as well as higher inter-individual variability. Here, we studied inter and intra-individual heterogeneity by exploring functional connectomes' variability and related it with clinical variables (PANSS Total scores and antipsychotic's doses). Our sample consisted of 30 patients with First Episode of Psychosis and 32 Healthy Controls, with a test–retest approach of two resting-state fMRI scanning sessions. In our patients' group, we found increased deviation from healthy functional connectomes and increased intragroup inter-subject variability, which was positively correlated to symptoms' levels in six subnetworks (visual, somatomotor, dorsal attention, ventral attention, frontoparietal and DMN). Moreover, changes in symptom severity were positively related to changes in deviation from healthy functional connectomes. Regarding intra-subject variability, we were unable to replicate previous findings of reduced connectome stability (i.e., increased intra-subject variability), but we found a trend suggesting that result. Our findings highlight the relevance of variability characterization in Schizophrenia, and they can be related to evidence of Schizophrenia patients having a noisy functional connectome.

1. Introduction

Schizophrenia is a heterogenous mental disorder with high variability in clinical profiles displayed by patients. Moreover, there is both inter-individual and intra-individual variability in Schizophrenia. In other words, not only two people diagnosed with this disorder may show different clinical presentations, but also a single patient may show different symptomatic patterns along their medical history (Kirkpatrick et al., 2001; Wong and van Tol, 2003).

Even in healthy populations, despite having gross similarities, brains of different individuals are unique (Barch et al., 2013; Gordon et al., 2017). Functional connectomes derived from fMRI studies capture such individual variability, and they have been shown to be stable in time, allowing for the identification of a particular subject among others, as if they were fingerprints (Finn et al., 2015; Amico and Goñi, 2018; Liu et al., 2018). However, traditional neuroimaging studies are advocated

to the estimation of mean group-level characteristics. As such, they fall short when assessing individual-level characteristics, which can be so relevant for a heterogenic and complex disorder such as Schizophrenia. For fMRI measures to provide insights into the clinical manifestations of Schizophrenia, they should correlate with variations in symptoms expression and, ideally, predict outcome, treatment response or risk of disease onset (van den Heuvel and Fornito, 2014).

There is evidence that functional connectomes' variability is associated with cognitive and behavioral variables (Barch et al., 2013). Several studies have used this information to predict individuals' performance variability in cognitive domains or symptom severity in neuropsychiatric disorders (Finn et al., 2015; Shen et al., 2017; Svaldi et al., 2021). Relatedly, the stability of a subject's functional connectome has been shown to be age-related: it increases during development, peaks in early adulthood, and decreases thereafter (Kaufmann et al., 2017; Ousdal et al., 2020). A delay in the stabilization of functional connectomes has been related to mental health in adolescents (Kaufmann et al., 2017).

Particularly, previous research suggests there is reduced connectome stability in patients with Schizophrenia, as the connectomic fingerprint of patients has been found to be less stable than that of healthy-control subjects (Kaufmann et al., 2018) This reduced stability of the connectome in Schizophrenia recalls the intra-individual clinical variability usually seen in patients. Moreover, it could be related to changes in symptom expression, although it has not been directly explored. In addition, inter-individual variability in Schizophrenia was also found to be higher in patients for whole brain analysis, frontoparietal, DMN, and ventral attention networks (Santo-Angles et al., 2021). Furthermore, this variability was negatively associated with PANSS scores (Santo-Angles et al., 2021), with more symptomatic patients being more similar to a patient's mean-connectome.

Regardless of their individually less stable connectomes, and in support of group-average traditional approaches, group-level mean functional connectomes have been shown to be useful for the classification of subjects with Schizophrenia (Ji et al., 2019; Talpalaru et al., 2019). Then, functional connectomes may also capture some common patterns of Schizophrenia, which make patients differ from healthy subjects. Functional connectomes can then capture subject-specific and group-average patterns, both of which are relevant for the future description of a Schizophrenia biomarker.

Here, we explored inter and intra-individual variabilities in a longitudinal sample (two resting state fMRI sessions) of patients with First Episode of Psychosis (FEP) and Healthy Controls (HC). In the patients' group, we looked for associations with clinical variables –particularly antipsychotic medication doses and symptoms severity (measured by Positive and Negative Syndrome Scale, PANSS). The early period of psychosis has been proposed as the most dynamic period of the illness (Birchwood et al., 1998), so studying variabilities and clinical changes in FEP patients, instead of looking for common group-patterns, can be a way to individualize subjects in their evolution throughout the disease. Based on previous literature, we expected to find reduced connectome stability (i.e., greater intra-individual variability and greater inter-individual variability) in psychotic patients.

2. Material and methods

2.1. Sample

Our data sample consisted of 30 patients with a First Episode of Psychosis (FEP), recruited at the Psychiatric Institute "Dr. José Horwitz Barak", in Santiago, Chile, and 32 Healthy Controls (HC). Patients fulfilled criteria for a psychotic episode according to the MINI neuropsychiatric interview (Lecrubier et al., 1997; Sheehan et al., 1998). Patients with a psychotic episode secondary to drugs abuse or a neurological or medical condition were excluded.

Each subject was scanned twice (two resting state fMRI sessions). In

the patients' group, the first scan was taken during their first psychotic episode (with a mean duration of treatment with antipsychotic medication of 23.83 ± 10.69 days) and the second scan, after 122.6 ± 44.22 days (or 17.51 ± 6.31 weeks) of treatment (Undurraga et al., 2022). In the case of healthy controls, the interval between scans was similar to that of patients (p = 0.605), with 128.87 ± 47. 59 days (or 18.3 ± 6.83 weeks).

Treatment was provided according to local guidelines and the clinical team's criteria, with no intervention from the research team. At both sessions, a psychiatrist assessed patients' symptoms with the PANSS scale (Stanley R Kay et al., 1987).

The study was approved by the Ethics and Research Committee of the Northern Metropolitan Health Service (SSMN) and the Ethics Committee of the Pontificia Universidad Católica de Chile. All participants signed informed consent.

2.2. Clinical variables

To compare doses of antipsychotic medication across patients taking different antipsychotic drugs, we used Chlorpromazine (CPZ) dose equivalents calculated according to Defined Daily Doses method (DDDs) (Leucht et al., 2016).

To assess symptoms severity, we used Positive and Negative Syndrome Scale (PANSS) (Stanley R Kay et al., 1987). This instrument is constituted by three subscales measuring positive and negative syndromes, and general psychopathology. The subscales are:
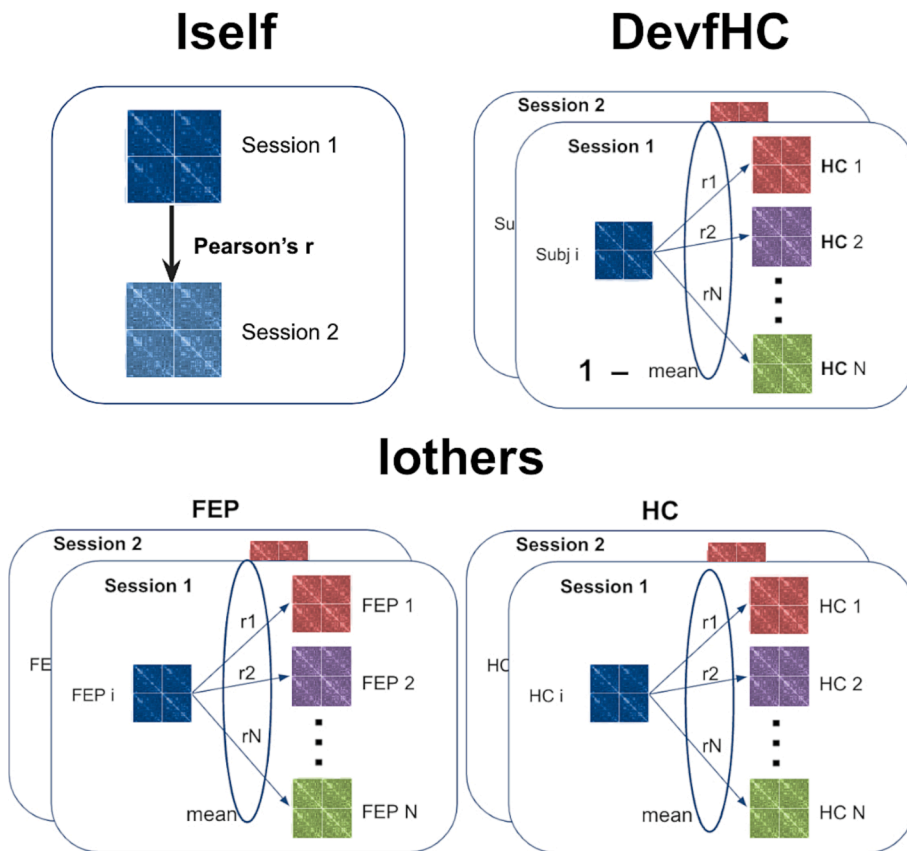
- Positive Scale (range 7 to 49): measures so-called positive symptoms, including delusions and hallucinations, which originally were conceptualized as productive features superadded to the mental status of patients.
- Negative Scale (range 7 to 49): measures negative symptoms such as a lack of motivation, conceptualized originally as deficit features characterized by loss of functioning.
- General Psychopathology (range 16 to 112): an important adjunct to the positive–negative assessment, to provide a parallel but separate measure of illness severity.

PANSS Total score (range 30 to 210) is obtained by summation across Positive, Negative and General Psychopathology subscales.

2.3. MRI protocol and preprocessing

Resting-state functional MRIs were acquired with a Philips Ingenia 3 T MRI scanner with a 16-channel brain coil. The scanning parameters were the following: total scan time 8.33 min, single-shot EPI, TR 2.5 s, TE 35 ms, flip angle of 82°, FOV of 220x220x110mm, and an isotropic spatial resolution of 2.75 mm. Subjects were asked to remain still and with their eyes opened. A structural T1-weighted image was also acquired with a voxel size of 1.0 mm3 isotropic, a TI delay of 965.2 ms, TE 3.6 ms, TR 7.7 ms, and flip angle of 8°.

Preprocessing of the functional images followed the same pipeline described elsewhere (Tepper et al., 2022), which includes usual steps of realignment and slice-time correction with SPM12 (Ashburner et al., 2021), co-registration and nonlinear transformation to MNI space with ANTs, (Avants et al., 2014), linear detrending, intensity normalization, spatial smoothing and bandpass-filtering (MATLAB, 2021). ICA-AROMA (Pruim et al., 2015) was used to remove residual movement artifacts, as well as the regression of mean white matter and cerebrospinal fluid. Also, one iteration of DiCER (Diffuse Cluster Estimation and Regression) (Aquino et al., 2020) with a full gray matter mask was implemented in order to correct biphasic global signal artifacts. This algorithm performs a clustering analysis of the voxels' time series to find wide-spread signal deflections (WSD); then it computes an adjusted-mean of such identified voxels, in which any anticorrelated voxel is flip around in sign. Finally, this adjusted mean of a detected WSD is regress-out to clean the BOLD

Iself

DevfHC

Iothers

signal. By using a full gray matter mask and one iteration in our implementation, we performed an adjusted version of Global Signal Regression (GSR), in which the flipping of anticorrelated voxels allows for correction of biphasic signal artifacts that are not cleaned-out by GSR, because its global mean value would turn out to be close to zero.

2.4. Analyses of functional connectomes

To define the ROIs in our functional connectomes, we used a 400 parcellations atlas (Schaefer et al., 2018) in which each parcel is matched to a corresponding network in the 7 Yeo networks (Yeo et al., 2014). We also incorporated a subcortical parcellation with 32 ROIs (Tian et al., 2020). For our analyses including subnetworks computations, 7 Yeo networks plus 1 subcortical 'network' were considered.

We computed functional connectomes (FC) by performing pairwise Pearson's correlations between time-series of the previously mentioned 432 ROIs. Fisher's z transform was applied to all subjects' FCs to get normal distributions of correlation values (Fisher, 1992) before computing our three variability measures (Deviation from Healthy FC, *Iself* and *Iothers*).

2.4.1. Intra-individual variability: Iself

We analyzed connectome stability to study whether patients' FCs change more than those from healthy controls from one session to the other (i.e., intra-subject variability).

Connectome stability was computed as the within-subject Pearson's correlation coefficient (i.e., Pearson's correlation between the two connectivity matrices from the same subject, taken in the two fMRI scan sessions) (see Fig. 1, top-left panel). This measure can also be referred to as the individual's fingerprint (Finn et al., 2015) or as *Iself* (Amico and Goñi, 2018), which will be used from now on. We computed *Iself* both from whole brain functional connectomes and separately from the 7 Yeo canonical functional networks (Yeo et al., 2014; Schaefer et al., 2018)

plus one additional 'network' of subcortical regions (Tian et al., 2020).

Then, we compared mean *Iself* values of FEP patients and HC on a group-level analysis. For these analyses, we modeled *Iself* with a GLM model including age, sex, days between sessions (SessInterval) and maximum framewise displacement (maximum value across the two mean values, each from one scan session) as covariates of no interest, and a categorical variable 'Group' with values 'FEP' or 'HC'. All numerical variables were standardized (centered and scaled) to aid in the interpretation of results.

Iself_network ~ Intercept + Age + Sex + maxFD + SessInterval + Group

Where *Iself_network* refers to either *Iself* computed from whole brain FC or subnetworks' FCs.

We used a second model, only with data from our patient's sample, to find out whether differences in connectome stability were related to clinical measures. Our predictors in this model were: deltaPANSS, which measured absolute changes in symptoms between the two sessions (measured as the absolute value of the inter-sessions difference of PANSS Total scores), and deltaAP, which measured absolute changes in treatment between the two sessions (measured as the absolute value of the inter-sessions difference of antipsychotic doses, APdose). Antipsychotic doses were expressed in mg of chlorpromazine (CPZ) equivalents using the DDD method (Leucht et al., 2016). As in the previous model, we included age, sex, days between sessions, and maximum framewise displacement as covariates of no interest, and all numerical variables were standardized to aid in the interpretation of results.

Iself_patient ~ Intercept + Age + Sex + maxFD + SessInterval + deltaPANSS + deltaAP

With: $deltaPANSS = abs(PANSSTot\_sess2 - PANSSTot\_sess1)$

and $deltaAP = abs(APdose\_sess2 - APdose\_sess1)$

2.4.2. Deviation from healthy FC

We then studied whether patients' FCs were more different to healthy FCs than HC intra-group differences. For this, we computed the "Deviation from Healthy FCs" (*DevfHC*) measure for each subject and each session as 1 minus the mean of pairwise Pearson's correlation between their connectome and each healthy subjects' FC, for the same session (see Fig. 1, top-right panel). As each subject has two FCs (one per session), we computed two *DevfHC* for each subject. Accordingly, we used the following mixed linear model for repeated measures to explore group differences in *DevfHC*:

DevfHC ~ Intercept + Age + Sex + FD + Group + (1|subject)

Where age and sex were time-invariant covariates (just one value was used for the repeated observations from a given subject), while FD was a time-varying covariate, taking on a different value (mean FD from session 1 or from session 2) for each of the repeated observations. We did not control for SessInterval in this model because *DevfHC* is computed independently for each session of each subject. All numerical variables were standardized to aid in the later interpretation of results.

Then, we tested whether different values of *DevfHC* in the FEP group were associated with clinical variables, specifically with symptoms levels (PANSS Total scores) and doses of antipsychotic medication (AP dose), with the following model:

DevfHC ~ Intercept + Age + Sex + FD + Total PANSS + AP dose + (1| subject)

In this model, both Total PANSS and AP dose were modeled as time-varying factors (with the corresponding values measured in each of the two sessions of each subject), to account for changes in between sessions. Antipsychotic doses were expressed in mg of chlorpromazine (CPZ) equivalents using the DDD method (Leucht et al., 2016), and all numerical variables were standardized before fitting the model.

In order to study how changes in clinical variables might relate to changes in *DevfHC*, we used the following model:

deltaDevfHC ~ Intercept + Age + Sex + FDmax + deltaPANSS_signed + deltaAPdose_signed

in which all 'delta' variables were computed as the difference between their value as measured in session 1 minus their value in session 2 (different from what we used in models for Iself values, in which we were not interested in the direction of the change, but only on its absolute value).

Here, then: deltaDevfHC = DevfHC_sess1 – DevfHC_sess2

deltaPANSS_signed = PANSSTotal_sess1 – PANSSTotal_sess2

deltaAP_signed = APdose_sess1 – APdose_sess2

Also, in this model we do not control for SessInterval because each value of *DevfHC* is computed by comparisons with healthy subjects on that same session. So, any physiological changes due to time will be present not only in the FC of each individual but also in those FCs with which we are comparing them.

2.4.3. Inter-individual variability: Iothers

To evaluate inter-individual differences between patients and controls, we used the fingerprint-like measure "*Iothers*" (as defined by Amico and Goñi, 2018), which can be calculated as the average of Pearson's correlations between pairs of connectivity matrices from different subjects from the same group. In other words, this is a measure of how much alike different subjects are in an intra-group fashion.

With our dataset, with two sessions per subject, we computed two measures of *Iothers* per subject as the average of Pearson's correlations

Table 1

Demographic and clinical information of the sample. Groups differed significantly in age, but not in sex, days between sessions nor framewise displacement. In the First Episode of Psychosis group (FEP), patients showed statistically significant differences in symptoms severity between sessions 1 and 2 (for PANSS Total scores and independently for each subscale). Not statistically significant changes were found in doses of antipsychotic medication between sessions.

	FEP (N = 30)		HC (N = 32)		Statistics
	Sess1	Sess2	Sess1	Sess2	
Sex (F/M)	8/22		13/19		Chi-square = 1.34 p = 0.246
Age (mean ± sd)	20.4 ± 2.57		24.06 ± 3.56		t = − 4.62 **p = 2.12e-05**
Days of treatment before first session (mean ± sd)	23.83 ± 10.69		NA		NA
Days between sessions 1 and 2 (mean ± sd)	122.6 ± 44.22 (17.51 ± 6.31 weeks)		128.87 ± 47.59 (18.3 ± 6.83 weeks)		t = 0.52 p = 0.605
PANSS Total score (mean ± sd)	68.83 ± 13.20	45.86 ± 15.27	NA	NA	t = 6.23 **p = 5.62e-08**
PANSS Positive scale (mean ± sd)	16.33 ± 6.18	10.10 ± 5.03	NA	NA	t = 4.29 **p = 6.93e-05**
PANSS Negative scale (mean ± sd)	19.93 ± 7.43	13.33 ± 7.13	NA	NA	t = 3.51 **p = 8.68e-04**
PANSS General scale (mean ± sd)	32.57 ± 6.69	22.43 ± 6.31	NA	NA	t = 6.04 **p = 1.18e-07**
Antipsychotic (AP) medication doses (CPZ equivalents in mg)	510.0 ± 303.81	450.36 ± 268.49	NA	NA	t = 0.79 p = 0.433
Mean Framewise Displacement (mean ± sd)	0.325 ± 0.129	0.318 ± 0.118	0.282 ± 0.071	0.322 ± 0.117	$t_{(FEPsess1, HCsess1)} = 1.64$ p = 0.106 $t_{(FEPsess2, HCsess2)} = -0.14$ p = 0.885

NA = Not Applicable. FEP = First Episode of Psychosis. HC = Healthy Controls.

between their own FC and those of the other subjects of the same group (see Fig. 1, bottom panel). For the case of HC group, *Iothers* is the inverse of *DevfHC*; but for FEP patients, *Iothers* is an intragroup inter-individual variability measure, whereas *DevfHC* is an intergroups inter-individual comparative measure. This is, *DevfHC* measured differences between patients and HC, and *Iothers* measured how different patients were among themselves.

We tested whether FEP patients had different *Iothers* than HC by means of the following mixed linear model (with all numerical variables standardized, and with FD as the only time-varying covariate). We did not control for SessInterval because *Iothers* is computed independently for each session of each subject.

Iothers ~ Intercept + Age + Sex + FD + Group + (1|subject)

Then, we evaluated whether different values of *Iothers* in FEP were related to clinical variables (both PANSS Total scores and doses of

Table 2

Summary of computed measures (whole brain FCs) and uncorrected group comparisons. We found no significant difference for Iself values between groups. Groups differed significantly in DevfHC and Iothers in session 1, but not in session 2.

	FEP (N = 30)		HC (N = 32)		Statistics
	Sess1	**Sess2**	**Sess1**	**Sess2**	
Iself (mean ± sd)	0.476 ± 0.087		0.508 ± 0.074		t = -1.58 p = 0.120
DevfHC (mean ± sd)	0.629 ± 0.035	0.630 ± 0.026	0.609 ± 0.033	0.621 ± 0.033	t $_{(FEPsess1, HCsess1)}$ = 2.36 **p = 0.021** t $_{(FEPsess2, HCsess2)}$ = 1.21 p = 0.230
Iothers (mean ± sd)	0.356 ± 0.033	0.368 ± 0.024	0.391 ± 0.033	0.379 ± 0.033	t $_{(FEPsess1, HCsess1)}$ = -4.13 **p = 0.0001** t $_{(FEPsess2, HCsess2)}$ = -1.41 p = 0.163

antipsychotic medication as time-varying factors) with the following model:

Iothers_patients ~ Intercept + Age + Sex + FD + Total PANSS + AP dose + (1|subject)

We also repeated these analyses computing *Iothers* from the 7 Yeo canonical functional networks (Yeo et al., 2014; Schaefer et al., 2018) plus the additional subcortical ROIs (Tian et al., 2020).

3. Results

Demographic and clinical information can be found in Table 1. Patients and healthy controls differed significantly in age (p = 2.12e-05). According to PANSS Total scores, and its correspondence to Clinical Global Impressions ratings (Leucht et al., 2005), our patients were "moderately ill" in session 1 and improved to "mildly ill" in session 2, with 122.6 ± 44.22 days of treatment in between sessions. Statistically significant differences between symptoms in sessions 1 and 2 were found for PANSS Total scores (p = 5.62e-08) and also for Positive, Negative and General subscales (p = 6.93e-05, p = 8.68e-04 and p = 1.18e-07, respectively). We modeled clinical symptoms severity by including PANSS Total scores in our models (results from models including PANSS subscales as separate factors can be found in Supplementary Information).

Where group comparisons were made between FEP and HC (models without inclusion of clinical variables), 1 HC subject was excluded due to missing values for days between sessions (N = 61, where N_{FEP} = 30 and N_{HC} = 31). In all FEP analyses including AP doses, 2 FEP subjects were excluded because of missing values (remaining N = 28).

3.1. General results

Summary of the computed measures and uncorrected group comparisons (2 sample *t*-test) can be found in Table 2. We found no differences in *Iself values* (p = 0.120), but patients differed significantly from healthy subjects in *DevfHC* and in *Iothers* in their first fMRI scanning session (p = 0.021 and p = 0.0001, respectively), but not in the second session (p = 0.230 and p = 0.163). Results from more refined analyses including confounds are described in the following sections.

Table 3

Models for Iself computed from whole brain FCs. Top table shows results for group comparisons (no statistically significant differences were found when correcting for age, sex, framewise displacement (FDmax) and days between sessions (SessInterval)). Bottom table shows model looking for associations with changes in clinical variables in the FEP group. No statistically significant results were found. All coefficients showed are standardized.

Iself ~ Age + Sex + FDmax + SessInterval + Group N = 61					
	Coef.	**Std.Err**	**t**	**P > |t|**	**[0.025–0.975]**
Intercept	0.2994	0.265	1.132	0.263	−0.231 – 0.829
Age	−0.1594	0.157	−1.014	0.315	−0.474 – 0.156
Sex[T.M]	−0.1328	0.286	−0.464	0.644	−0.706 – 0.440
FDmax	−0.2345	0.137	−1.709	0.093	−0.509 – 0.040
SessInterval	0.0304	0.129	0.235	0.815	−0.229 – 0.289
Group[T.FEP]	−0.4317	0.298	−1.447	0.154	−1.029–0.166

| Iself_patients ~ Age + Sex + FDmax + SessInterval + deltaPANSS + deltaAPdose N = 28					
	Coef. (std)	**Std.Err**	**t**	**P > |t|**	**[0.025–0.975]**
Intercept	−0.0478	0.418	−0.114	0.910	−0.916 – 0.821
Age	−0.2098	0.227	−0.925	0.365	−0.681 – 0.262
Sex[T.M]	0.0669	0.520	0.129	0.899	−1.014 –1.148
FDmax	−0.1155	0.217	−0.532	0.600	−0.567 – 0.336
SessInterval	0.1852	0.227	0.814	0.425	−0.288 – 0.658
deltaPANSS	−0.1886	0.214	−0.883	0.387	−0.633 – 0.225
deltaAPdose	0.3332	0.205	1.629	0.118	−0.092 – 0.759

Table 4

Iself subnetworks: groups comparison. Summary of results for categorical variable 'Group', across models for Iself values computed from subnetworks. Uncorrected p values point to significant group differences in somatomotor, frontoparietal and DMN networks, with reduced Iself values in patients. No results remain significant after correction for multiple comparisons with FDR Benjamini & Hochberg. All coefficients showed are standardized.

Iself_network	Group (T.FEP)		
	Coefficient	*Uncorrected p*	*Corrected p (fdr)*
Whole brain	−0.4317	0.154	——
Visual	−0.0157	0.956	0.956
Somatomotor	−0.6193	**0.040**	0.106
Dorsal Attention	−0.4891	0.105	0.210
Ventral Attention	−0.4374	0.149	0.239
Limbic	−0.3526	0.255	0.340
Frontoparietal	−0.6249	**0.023**	0.106
DMN	−0.6301	**0.030**	0.106
Subcortical	−0.1092	0.715	0.817

3.2. Intra-individual variability: Iself

As it can be seen in Tables 3 and 4, we found no group differences for whole brain functional connectomes (Group p-val = 0.154). Uncorrected p values point to a significant effect of Group for Iself values from somatomotor, frontoparietal and DMN network, but none of them survives multiple comparisons correction (FDR Benjamini & Hochberg). The direction was similar *for lower Iself* in FEP patients for all subnetworks (see Table 4 and Fig. 2).

Results from modelling *Iself* values with clinical variables can be seen in Table 3 (whole brain) and Table 5 (all networks). For these models, no results were statistically significant after correcting for multiple comparisons with FDR Benjamini & Hochberg method. When substituting in the model the predictor deltaPANSS by its three subscales (deltaPositive, deltaNegative and deltaGeneral), results suggest a significant association between changes in General PANSS subscale and Iself values in Ventral Attention networks. For more details on those results see Supplementary information (Table S1 and S2).
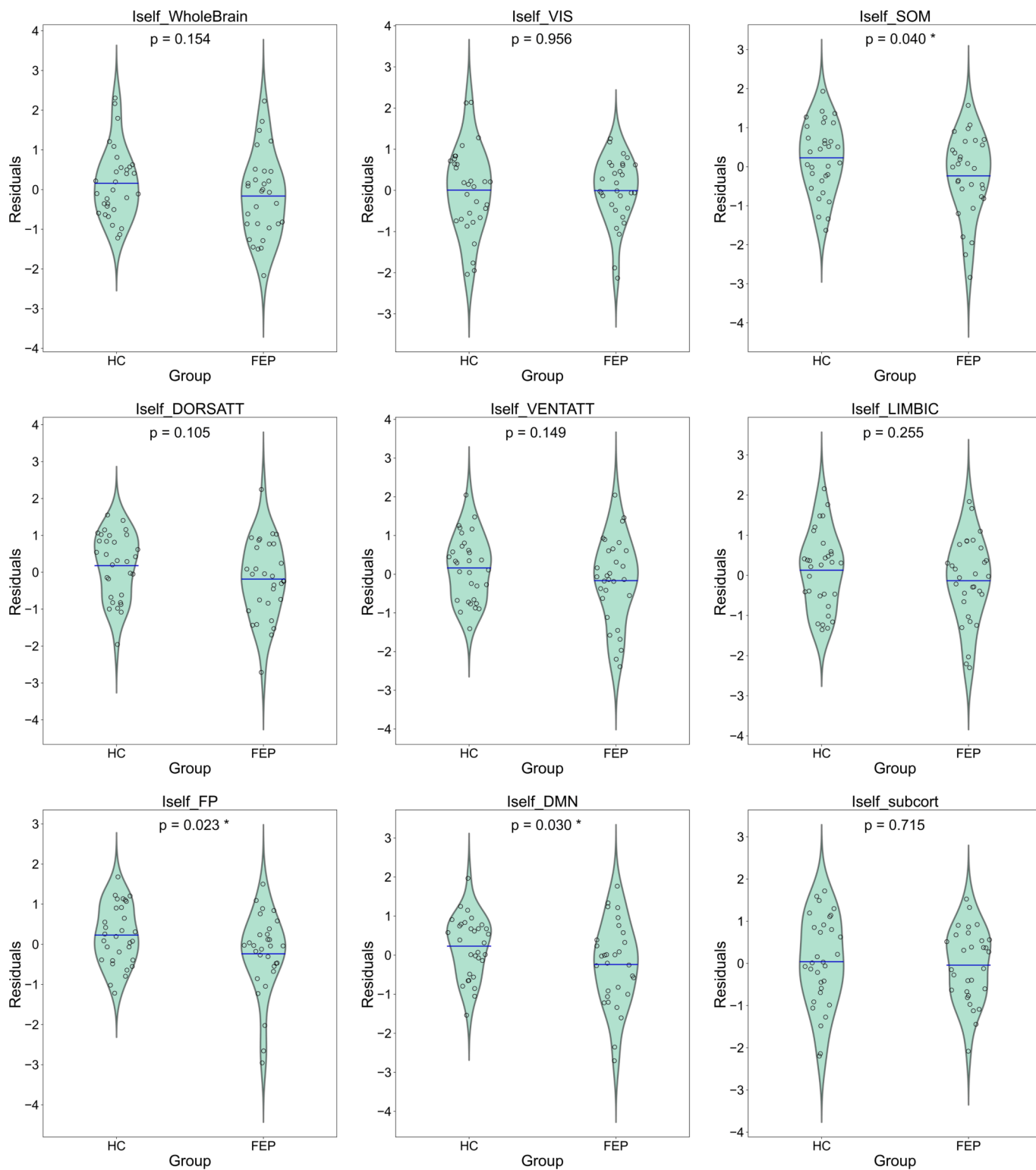
Fig. 2. Residualized Iself group differences. Residuals from model Iself ~ Intercept + Age + Sex + FD + SessInterval (all numerical variables standardized) plotted according to Group (FEP or HC). Blue line represents the mean value of the distribution. Shown p-values correspond to uncorrected p-values for 'Group' beta co-efficient from linear models with Iself as dependent variable (* highlights p < 0.05) (See Table 4). Uncorrected p values point to significant group differences in somatomotor, frontoparietal and DMN networks, with reduced Iself in patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Deviation from healthy FC

We found a significant association between Deviation from healthy connectomes (*DevfHC*) and being in the FEP group (standardized beta of 0.491 ± 0.237, p = 0.038; Table 6 top panel), controlling for differences in sex, age and framewise displacement. We also looked at whether this association was related to clinical variables. As shown in Table 6 (bottom panel), we did not find significant associations (p values for

Table 5

Iself subnetworks: models with clinical variables. Summary of results for variables 'deltaPANSS' and 'deltaAP' (see Methods) across models for Iself values computed from subnetworks, and only for FEP subjects. Uncorrected p values point to significant associations between deltaPANSS and Iself from Ventral Attention network, and between deltaAPdose and Visual, Ventral Attention and Frontoparietal networks. No results remain significant after correction for multiple comparisons with FDR Benjamini & Hochberg. All coefficients showed are standardized.

Iself_patients	deltaPANSS			deltaAPdose		
	Coefficient	Uncorrected p	Corrected p (fdr)	Coefficient	Uncorrected p	Corrected p (fdr)
Whole brain	−0.1886	0.387	——	0.3332	0.118	——
Visual	−0.1251	0.534	0.611	0.4743	**0.021**	0.092
Somatomotor	−0.1070	0.642	0.642	0.3210	0.154	0.206
Dorsal Attention	−0.1509	0.456	0.611	0.1747	0.369	0.422
Ventral Attention	−0.4886	**0.018**	0.146	0.4142	**0.034**	0.092
Limbic	0.1876	0.394	0.611	0.3278	0.127	0.203
Frontoparietal	0.1246	0.513	0.611	0.4054	**0.032**	0.092
DMN	−0.1610	0.445	0.611	0.3214	0.120	0.203
Subcortical	0.1446	0.500	0.611	−0.0057	0.978	0.978

Table 6

Results for DevfHC mixed models. Top table shows results for group comparisons: FEP subjects showed greater DevfHC when correcting for age, sex and framewise displacement (FD) (p = 0.038). Bottom table shows model looking for associations with clinical variables in the FEP group. No statistically significant results were found. All coefficients showed are standardized.

DevfHC ~ Age + Sex + FD + Group + (1|subject) N = 61					
	Coef.	Std. Err	z	P > |z|	[0.025 – 0.975]
Intercept	−0.152	0.209	−0.727	0.467	−0.563 – 0.258
Age	0.033	0.122	0.275	0.783	−0.205 – 0.272
Sex[T.M]	−0.136	0.224	−0.610	0.542	−0.575 – 0.302
FD	0.027	0.088	0.307	0.759	−0.145 – 0.199
Group[T.FEP]	0.491	0.237	2.071	**0.038**	0.026 – 0.957
Group Var (random factor)	0.288	0.199			

DevfHC ~ Age + Sex + FD + TotalPANSS + APdose + (1|subject) N = 28					
	Coef.	Std. Err	z	P > |z|	[0.025 – 0.975]
Intercept	0.288	0.256	1.124	0.261	−0.214 – 0.790
Age	0.096	0.135	0.709	0.478	−0.169 – 0.360
Sex[T.M]	−0.403	0.310	−1.301	0.193	−1.011 – 0.204
FD	−0.169	0.134	−1.264	0.206	−0.432 – 0.093
Total PANSS	0.197	0.132	1.489	0.136	−0.062 – 0.456
APdose	0.264	0.141	1.878	0.060	−0.011 – 0.539
Group Var (random factor)	0.000	0.201			

Table 7

Results for deltaDevfHC models. Top table shows results for group comparisons: no statically significant difference were found when accounting for age, sex and framewise displacement (FDmax). Bottom table shows model looking for associations with changes in clinical variables in the FEP group: deltaPANSS_signed was positively associated with deltaDevfHC (p = 0.035). All coefficients showed are standardized.

deltaDevfHC ~ Age + Sex + FDmax + Group N = 61					
	Coef.	Std. Err	t	P > |t|	[0.025 – 0.975]
Intercept	−0.3122	0.269	−1.161	0.250	−0.851 – 0.226
Age	0.1030	0.160	0.646	0.521	−0.217 – 0.423
Sex[T.M]	0.2318	0.290	0.799	0.428	−0.349 – 0.813
FDmax	0.1127	0.139	0.809	0.422	−0.167 – 0.392
Group[T.FEP]	0.3256	0.303	1.075	0.287	−0.281 – 0.932

| deltaDevfHC ~ Age + Sex + FDmax + deltaPANSS_signed + deltaAPdose_signed N = 28					
	Coef.	Std. Err	t	P > |t|	[0.025 – 0.975]
Intercept	0.0063	0.388	0.016	0.987	−0.799 – 0.811
Age	−0.2057	0.220	−0.935	0.360	−0.662 – 0.250
Sex[T.M]	−0.0089	0.474	−0.019	0.985	−0.992 – 0.974
FDmax	−0.0222	0.209	−0.106	0.916	−0.455 – 0.411
deltaPANSS_signed	0.4906	0.218	2.254	**0.035**	0.039 – 0.942
deltaAPdose_signed	0.1660	0.206	0.806	0.429	−0.261 – 0.593

3.4. Inter-individual variability: Iothers

Regarding *Iothers* (i.e., how similar a subject is to their group), we found a statistically significant difference between groups (p = 0.001), after controlling for sex, age and movement within the scanner. FEP patients showed reduced *Iothers* values (more inter-subject variability) with standardized beta coefficient of −0.716.

Then, we tested whether these differences in whole brain *Iothers* of FEP patients were attributable to clinical differences (PANSS Total score and doses of antipsychotic medication). When correcting for age, sex and framewise displacement, we found a statistically significant association with PANSS Total scores (p = 0.027) and a trending association with AP doses (p = 0.057) (see Fig. 4). We also found an association between *Iothers* and sex, with male subjects being more similar to other patients (p = 0.049). More information about these analyses can be

variables Total PANSS and APdose were 0.136 and 0.060 respectively). Results looking at PANSS subscales were similar and can be found in Supplementary information (Table S3).

When assessing changes in *DevfHC* (*deltaDevfHC*), we found no group differences (see Table 7). However, in the group of patients, we found a positive association between *deltaPANSS_signed* and *deltaDevfHC* (p = 0.035) (see Table 7 and Fig. 3). Results looking at PANSS subscales suggest this association to be mainly attributable to changes in Negative symptoms (see Table S4).

Fig. 3. Model fit for deltaDevfHC and association with deltaPANSS_signed. The positive association between deltaDevfHC and deltaPANSS_signed is colour coded. deltaDevfHC was positively associated with deltaPANSS_signed when accounting for age, sex, FDmax and deltaAPdose_signed (p = 0.035). See Table 7 for more information on this model.
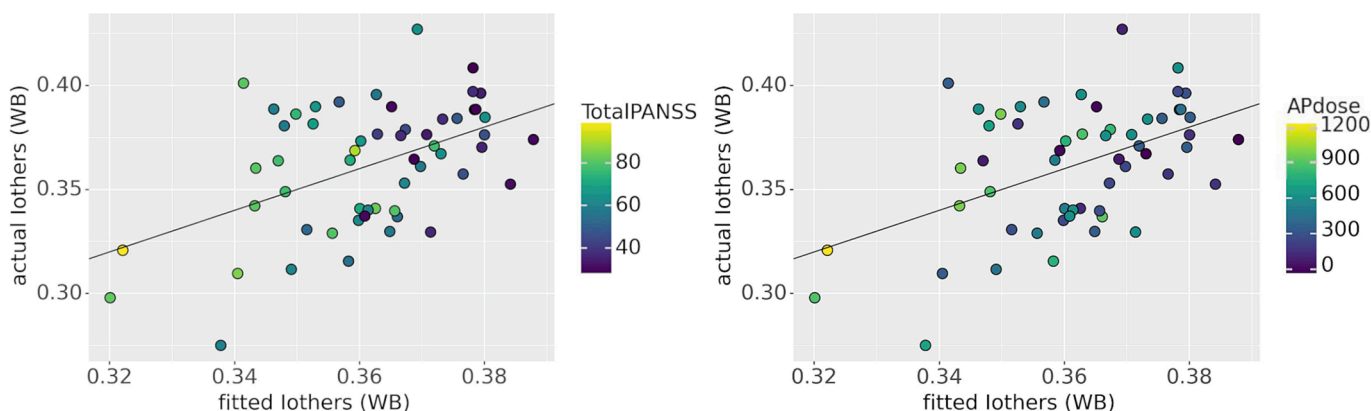
Fig. 4. Model fit for Iothers (whole brain) and association with clinical variables. Associations between Iothers WB (whole brain) and clinical variables are colour coded. Left panel: Iothers and PANSS Total scores were negatively associated (p = 0.027). Right panel: Iothers and AP doses showed a trend to a negative association (p = 0.057). For more information on this model see Table 8.

found in Table 8.

We then analyzed *Iothers* computed from subnetworks. After controlling for sex, age, and movement within the scanner, and correcting for multiple comparisons (FDR Benjamini & Hochberg), we found a significant group difference in all 7 Yeo networks (but not for subcortical regions) (see Table 9). As it can be seen in Table 8, for all significant subnetworks, FEP patients showed reduced *Iothers* values (more inter-subject variability). Residualized *Iothers* group differences (correcting for sex, age and FD) can be seen in Fig. 5.

In 6 out of these 7 networks (visual, somatomotor, dorsal attention, ventral attention, frontoparietal and DMN), *Iothers* was negatively correlated with PANSS Total scores (more symptomatic patients would be more different from other patients) (see Table 10). Associations with AP doses did not reach statistical significance. Results looking at PANSS subscales suggest associations between changes in Negative symptoms and Iothers computed from whole brain, as well as somatomotor and ventral attention networks (see Table S5 and S6).

4. Discussion

In this study, we explored inter and intra-individual variabilities in a group of subjects with First Episode of Psychosis (FEP) using resting state fMRI data and fingerprint-like measures derived from functional connectomes. Particularly, we explored three measures: *Iself,* Deviation

from Healthy FC, and *Iothers*.

As mentioned in the introduction, it has been previously reported that adults with Schizophrenia spectrum disorders have decreased connectome stability (Kaufmann et al., 2018). We expected our results to replicate such increased intra-subject variability, but no statistically significant values emerged from our analysis of *Iself* measures (whole brain p-value = 0.154). However, the tendency of all of our comparisons pointed in the same direction as previously reported findings, showing reduced *Iself* for FEP patients. Moreover, uncorrected p-values (without correcting for multiple comparisons) showed three Schizophrenia-relevant networks as focuses of reduced connectome stability (i.e., somatomotor, frontoparietal and DMN networks).

Even if our results did not back up inter-group differences in connectome stability, the idea of greater intra-individual variability inevitably recalls the clinical variability seen in patients with Schizophrenia. As such, we decided to explore whether intra-group differences in *Iself* were associated to changes in symptoms (as measured by PANSS Total scores) and/or changes in antipsychotic doses from one session to the other (with a few months of treatment in between) in our FEP sample. If changes of symptomatology scores (or medication doses) were related to *Iself* in a negative direction, this could imply that patients who remain more stable in a certain clinical status have greater congruence with their own FC from a different session. However, our results were not statistically significant and therefore the data did not support this

Table 8

Models for Iothers computed from whole brain FCs. Top table shows results for group comparisons: FEP subjects showed reduced Iothers when accounting for age, sex and framewise displacement (FD) (p = 0.001). Bottom table shows model looking for associations with clinical variables in the FEP group: PANSS Total score was negatively associated with Iothers (p = 0.027), and male subjects had higher Iothers values (p = 0.049). All coefficients showed are standardized.

Iothers ~ Age + Sex + FD + Group + (1|subject)				
N = 61				
	Coef.	Std. Err	z	P > |z|	[0.025 – 0.975]
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Intercept	0.216	0.198	1.091	0.275	−0.172 – 0.604
Age	−0.021	0.115	−0.187	0.852	−0.247 – 0.204
Sex[T.M]	0.208	0.211	0.982	0.326	−0.207 – 0.622
FD	−0.029	0.086	−0.337	0.736	−0.197 – 0.139
Group[T.FEP]	−0.716	0.224	−3.193	**0.001**	−1.156 – −0.276
Group Var (random factor)	0.224	0.179			

Iothers_patients ~ Age + Sex + FD + TotalPANSS + APdose + (1|subject)				
N = 28				
	Coef.	Std. Err	z	P > |z|	[0.025 – 0.975]
---	---	---	---	---	---
Intercept	−0.419	0.246	−1.703	0.089	−0.900 – 0.063
Age	−0.076	0.129	−0.587	0.557	−0.329 – 0.177
Sex[T.M]	0.586	0.297	1.970	**0.049**	0.003 – 1.169
FD	0.141	0.128	1.099	0.272	−0.111 – 0.393
Total PANSS	−0.286	0.129	−2.217	**0.027**	−0.539 – −0.033
APdose	−0.259	0.136	−1.905	0.057	−0.526 – 0.007
Group Var (random factor)	0.000	0.205			

Table 9

Iothers subnetworks: groups comparison. Summary of results for variable 'Group' across models for Iothers computed from subnetworks. Before and after correction for multiple comparisons with FDR Benjamini & Hochberg, FEP subjects showed reduced Iothers when computed from whole brain functional connectomes and also from all 7 Yeo networks, but not for subcortical regions. All coefficients showed are standardized.

Iothers_network	Group (T.FEP)		
	Coefficient (beta std)	Uncorrected p	Corrected p (fdr)
Whole brain	−0.716	**0.001**	——
Visual	−0.505	**0.024**	**0.038**
Somatomotor	−0.966	**0.000**	**0.000**
Dorsal Attention	−0.691	**0.001**	**0.001**
Ventral Attention	−1.024	**0.000**	**0.000**
Limbic	−0.473	**0.031**	**0.041**
Frontoparietal	−0.462	**0.022**	**0.038**
DMN	−0.423	**0.042**	**0.048**
Subcortical	−0.022	0.922	0.922

interpretation.

Regarding inter-individual variance, first, with our measure of Deviation from Healthy FC, we studied individual mean distance to healthy functional connectomes. As expected, we found greater distances in the patients' group (p = 0.038). This result means that patients' FCs are generally more different from healthy FC than those of other healthy subjects. However, when analyzing our patients' group, our results were not conclusive regarding whether this distance to healthy FCs is

associated to symptoms severity or medication doses, although patients who were more medicated seem to differ more (with trend p value 0.060 for antipsychotic doses).

Relatedly, we also evaluated *deltaDevfHC* to analyze not only the relationship between illness severity and the distance to healthy FC, but how changes in clinical variables affect such distance. In this case, we found no group differences (p = 0.287), meaning patients and controls distances to healthy FCs changed approximately the same from session 1 to session 2 (there might be healthy physiological changes in between sessions). However, we did find a positive association in the patients' group between *deltaPANSS_signed* and *deltaDevfHC* (p = 0.035). Patients whose symptoms were reduced from session 1 to session 2 (deltaPANSS_signed > 0), got closer to healthy FCs (*deltaDevfHC* > 0) (recall from Methods that delta is computed as DevfHC_Sess1 – DevfHC_Sess2, so a positive value means that distance was larger in session 1). According to analyses with PANSS subscales as covariables, this associations might be mainly driven by changes in Negative symptoms (see Table S4).

The idea of Deviation from Healthy FC can be related to previous studies in which group-level mean functional connectomes help classify subjects with Schizophrenia (Ji et al., 2019). In this matter, machine learning techniques have been used to train relatively successful classifiers (with an average of 75% accuracy) to distinguish between patients and healthy controls based on their functional connectomes (Ji et al., 2019; Talpalaru et al., 2019). Results of such classification studies are usually interpreted as the same phenotypic group having some similar functional connectome features (as connectivity signatures), which are used by the trained algorithms to discriminate among subjects of different groups. Then, functional connectomes of Schizophrenia patients may have some distinct patterns which make them different from healthy subjects, and our results point to clinical variables (particularly symptoms severity) being related to changes in these abnormal patterns.

Regarding inter-individual variance, we also explored whether patients are more (or less) similar than healthy controls in an intra-group comparison. By evaluating group differences of *Iothers* (i.e., how much similar a subject is to their group) computed from whole brain FCs, we found a statistically significant difference (p = 0.001), with FEP patients showing reduced *Iothers* values (more inter-subject variability). We also found a statistically significant association with PANSS score (p = 0.027), and a trending association with AP doses (p = 0.057), which indicates that patients with higher PANSS scores (and higher AP doses) have lower values of *Iothers* (they are less similar to other patients). We also found an association with sex (p = 0.049), indicating male patients to be more similar to other patients; which might be related to the fact that 73% of our patients are men (Ritchie et al., 2018).

When analyzing *Iothers* from subnetworks, we found a group difference for *Iothers* in all 7 Yeo networks (but not for subcortical regions). In all subnetworks, FEP patients showed higher inter-subject variability (reduced *Iothers*), which in 6 networks (visual, somatomotor, dorsal attention, ventral attention, frontoparietal and DMN) was correlated with PANSS Total scores (the more symptomatic, the more different to other patients). According to analyses with PANSS subscales as covariables, these associations might be mainly driven by Negative symptoms (see supplementary information). Associations with AP doses did not reach statistical significance.

A recent study exploring inter-individual variability in Schizophrenia found a similar result of higher variability in patients in whole brain and in frontoparietal, DMN, and ventral attention networks (Santo-Angles et al., 2021). However, in that study they found an opposite association with symptomatology: more symptoms were associated with more similar connectomes (Santo-Angles et al., 2021). The authors argued that more symptomatic patients may be overrepresented in their mean connectome, which they used for assessing interindividual similarity. When exploring inter-individual variability in an intragroup fashion, we should keep in consideration that outcomes will
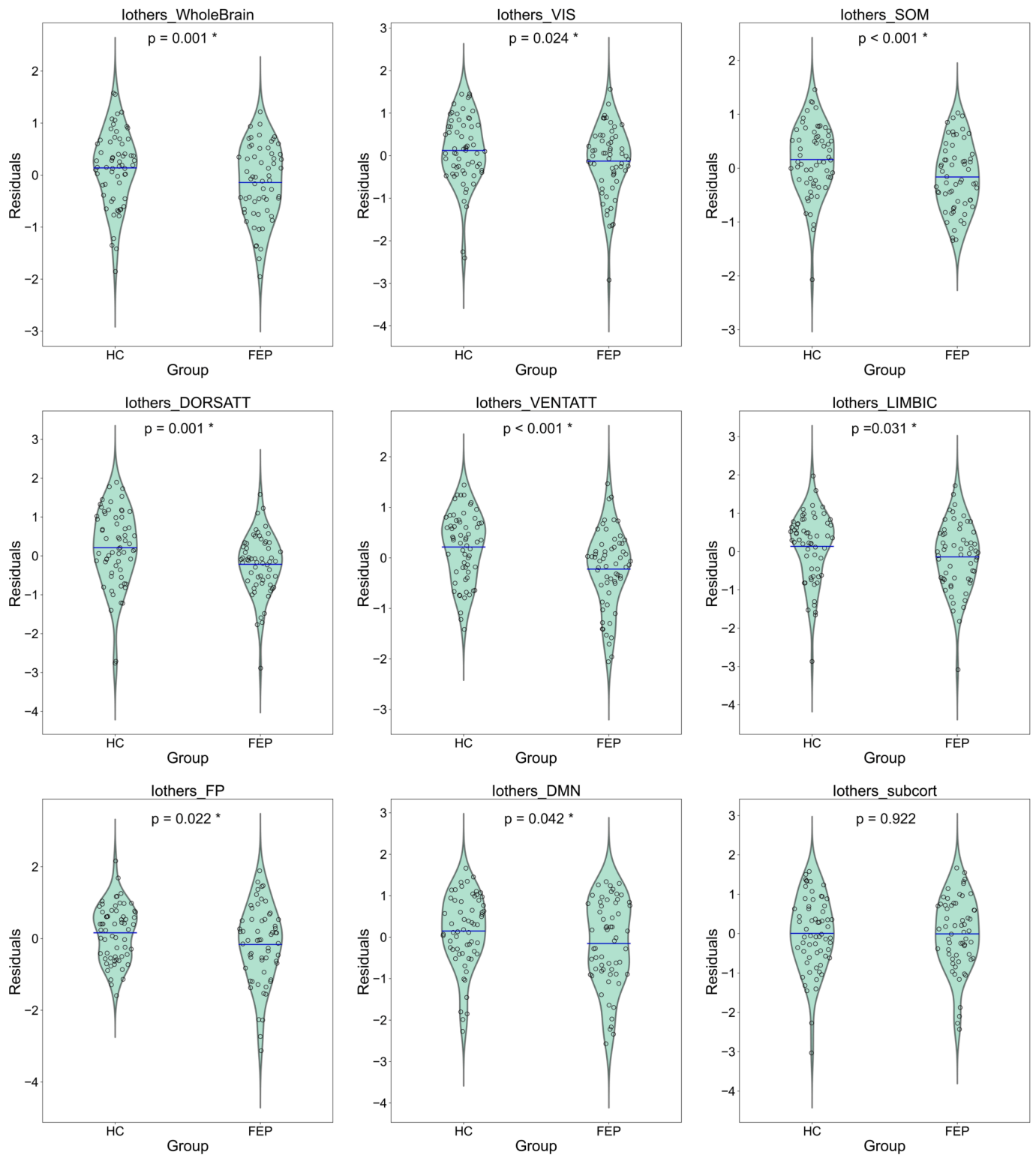
Fig. 5. Residualized Iothers group differences. Residuals from model Iothers ~ Age + Sex + FD + (1|subject) (all numerical variables standardized) plotted according to Group (FEP or HC). Blue line represents the mean value of the distribution. Shown p-values correspond to uncorrected p-values for 'Group' beta co-efficient from mixed models with Iothers as dependent variable (* highlights p < 0.05) (See Table 9). FEP subjects showed reduced Iothers when computed from whole brain functional connectomes and also from all 7 Yeo networks, but not for subcortical regions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

depend on the nature of our samples (this is, who we are comparing each subject against). Particularly, when regarding associations with clinical variables, the degree and heterogeneity in illness severity of the sample under study might have an impact on the direction of results. Here we computed *Iothers* by pairwise comparisons between subjects (and later we took the average of those values), and our results point to more symptomatic patients having a greater difference to others in their group.

Table 10

Iothers subnetworks: models with clinical variables. Summary of results for variables 'TotalPANSS' and 'APdose' across models for Iothers computed from subnetworks, and only for FEP subjects. After correction for multiple comparisons with FDR Benjamini & Hochberg, Iothers was negatively associated to TotalPANSS when computed from whole brain as well as networks Visual, Somatomotor, Dorsal Attention, Ventral Attention, Frontoparietal and DMN. No significant associations between Iothers and APdose were found. All coefficients showed are standardized.

Iothers_network	TotalPANSS			APdose		
	Coefficient	Uncorrected p	Corrected p (fdr)	Coefficient	Uncorrected p	Corrected p (fdr)
Whole brain	−0.286	**0.027**	——	−0.259	0.057	——
Visual	−0.304	**0.026**	**0.035**	−0.131	0.348	0.901
Somatomotor	−0.303	**0.016**	**0.026**	−0.015	0.917	0.917
Dorsal Attention	−0.355	**0.005**	**0.013**	0.066	0.612	0.901
Ventral Attention	−0.417	**0.001**	**0.005**	0.040	0.762	0.901
Limbic	−0.096	0.557	0.557	−0.125	0.445	0.901
Frontoparietal	−0.534	**0.000**	**0.001**	−0.083	0.520	0.901
DMN	−0.359	**0.009**	**0.018**	−0.036	0.788	0.901
Subcortical	−0.205	0.135	0.154	−0.169	0.215	0.901

Our findings of higher variability in FEP patients are consistent with the heterogeneity of the disorder and could be related to studies showing that Schizophrenia subjects have noisier (i.e., more variable) brains. There have been studies using entropy measures, which related Schizophrenia with more complex signal patterns than healthy subjects and dysregulation of brain dynamics (Sokunbi et al., 2014). Also, biologically realistic computational models have shown how Schizophrenia is characterized by diminished signal-to-noise ratios (Rolls et al., 2008). These models have shown that neurons firing irregularly and less synchronized, would be reflected in a more variable (that is, noisier) BOLD signal (Rolls et al., 2008). Both findings of higher intra and inter-individual variabilities in Schizophrenia would be consistent with such an assumption.

These non-uniformly distributed variabilities of functional features in Schizophrenia can lead to biased results in group-means comparisons. In healthy subjects, intra-subject variability is concentrated in visual and somatomotor regions (Laumann et al., 2015; Poldrack et al., 2015), while inter-subject variability has been shown to be significantly higher in multimodal association areas and lower in unimodal sensory and primary motor areas (Mueller et al., 2013). Our findings of reduced connectome stability (with uncorrected p-values) showed that patients would have higher intra-subject variability in frontoparietal, DMN, and somatomotor networks. On top of that, our results showed higher inter-subject variability for patients across all cortical networks. In particular, inter-subject variability can be a crucial factor for group-means comparisons, where brain regions with low inter-subject variability reach with higher probability the cut-off for significance than regions with higher inter-subject variability (Zilles and Amunts, 2013).

Our results here show that there is increased inter-individual variability in FEP patients, both intragroup and when comparing them to healthy subjects. Moreover, inter-individual variability between patients seems to be associated with illness severity, with connectomes from more symptomatic patients differing more. This resonates with results from studies looking at more chronic patients (Kaufmann et al., 2018; Santo-Angles et al., 2021), and extends them to the first period of the illness, where changes are more dynamic (Birchwood et al., 1998). Our findings could support the theory of a noisy connectome. If neurotransmitter dysregulations result in reduced signal-to-noise ratios, then the information captured by functional connectomes would also be noisy and any comparisons like the ones made here would result in greater variabilities.

Limitations

This study has some limitations worth noting. First, our analyses (particularly for *Iself*) could have been underpowered (see Supplementary Information for power analysis and sample size estimation). *Iself* is the only measure in which no averaging (which increases signal-to-noise ratios) is done at any point of the computation. Moreover, statistical models for Iself values do not have repeated measures, since only one measure of *Iself* is obtained for each subject from the two repeated scans.

These methodological characteristics would require analyses to have larger sample sizes to reach same levels of statistical power. Kaufmann et al., 2018 found reduced connectome stability in Schizophrenia patients using a sample>5 times larger than the one used here (Number of patients = 167, Number of controls = 202). Similarly, Santo-Angles et al., 2021 assessed inter individual variability in 110 patients and 110 control subjects.

On top of that, in this study we computed *Iself* and *Iothers* using Pearson's correlation of full connectomes (or complete subnetworks). Some other more spatially localized measures (such as Regional Homogeneity - ReHo) have been shown to more strongly identify subjects (even from Schizophrenia samples) (Larabi et al., 2022). Future studies could examine more localized metrics from a fingerprint perspective.

5. Conclusions

We showed a trend towards reduced connectome stability (i.e., increased intra-subject variability). We found increased deviation from healthy FCs in patients with first episode of psychosis, whose changes were related to changes in symptoms severity; and we found increased intragroup inter-subject variability which was related to symptoms' levels in 6 Yeo networks (visual, somatomotor, dorsal attention, ventral attention, frontoparietal and DMN).

In the search for a Schizophrenia biomarker, and given the heterogeneity of this disorder, it is highly relevant to find individual-level measures which relate to clinical aspects. We here showed that the functional connectome can capture individual variability related to the severity of the disorder. However, it is possible that some of our analyses were underpower. Further research is needed to shed light on the real prognostic value of functional connectome's variability.

Data and code availability

Functional connectomes and behavioral data used in this work is available in Zenodo https://doi.org/10.5281/zenodo.7569166

Code used for analyses is available in this GitHub repository: https://github.com/angietep/Inter-and-Intra-Indiv-Variability

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is available from Zenodo and scripts from Github,as described in the paper (see Conclusions).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103391.

References

Amico, E., Goñi, J., 2018. The quest for identifiability in human functional connectomes. Sci Rep 8, 1–14. https://doi.org/10.1038/s41598-018-25089-1.

Aquino, K.M., Fulcher, B.D., Parkes, L., Sabaroedin, K., Fornito, A., 2020. Identifying and removing widespread signal deflections from fMRI data: Rethinking the global signal regression problem. Neuroimage 212, 116614. https://doi.org/10.1016/J.NEUROIMAGE.2020.116614.

Ashburner, J., Barnes, G., Chen, C.-C., Daunizeau, J., Flandin, G., Friston, K., Gitelman, D., Glauche, V., Henson, R., Hutton, C., Jafarian, A., Kiebel, S., Kilner, J., Litvak, V., Mattout, J., Moran, R., Penny, W., Phillips, C., Razi, A., Stephan, K., Tak, S., Tyrer, A., Zeidman, P., 2021. SPM12 manual. researchgate.net.

Avants, B.B., Tustison, N., Johnson, H., 2014. Advanced Normalization Tools (ANTS) Release 2.x.

Barch, D.M., Burgess, G.C., Harms, M.P., Petersen, S.E., Schlaggar, B.L., Corbetta, M., Glasser, M.F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J.M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A.Z., van Essen, D.C., 2013. Function in the human connectome: Task-fMRI and individual differences in behavior. Neuroimage, Mapping the Connectome 80, 169–189. https://doi.org/10.1016/j.neuroimage.2013.05.033.

Birchwood, M., Todd, P., Jackson, C., 1998. Early intervention in psychosis: The critical period hypothesis. The British Journal of Psychiatry 172, 53–59. https://doi.org/10.1192/S0007125000297663.

Finn, E.S., Shen, X., Scheinost, D., Rosenberg, M.D., Huang, J., Chun, M.M., Papademetris, X., Constable, R.T., 2015. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat Neurosci 18, 1664–1671. https://doi.org/10.1038/nn.4135.

Fisher, R.A., 1992. Statistical Methods for Research Workers 66–70. 10.1007/978-1-4612-4380-9_6.

Gordon, E.M., Laumann, T.O., Adeyemo, B., Petersen, S.E., 2017. Individual Variability of the System-Level Organization of the Human Brain. Cereb Cortex 27, 386–399. https://doi.org/10.1093/cercor/bhv239.

Ji, G.J., Chen, X., Bai, T., Wang, L., Wei, Q., Gao, Y., Tao, L., He, K., Li, D., Dong, Y., Hu, P., Yu, F., Zhu, C., Tian, Y., Yu, Y., Wang, K., 2019. Classification of schizophrenia by intersubject correlation in functional connectome. Hum Brain Mapp 40, 2347–2357. https://doi.org/10.1002/hbm.24527.

Kaufmann, T., Alnæs, D., Doan, N.T., Brandt, C.L., Andreassen, O.A., Westlye, L.T., 2017. Delayed stabilization and individualization in connectome development are related to psychiatric disorders. Nat Neurosci 20, 513–515. https://doi.org/10.1038/nn.4511.

Kaufmann, T., Alnæs, D., Brandt, C.L., Bettella, F., Djurovic, S., Andreassen, O.A., Westlye, L.T., 2018. Stability of the Brain Functional Connectome Fingerprint in Individuals With Schizophrenia. JAMA Psychiatry 75, 749–751. https://doi.org/10.1001/JAMAPSYCHIATRY.2018.0844.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13, 261–276.

Kirkpatrick, B., Buchanan, R.W., Ross, D.E., Carpenter, J., 2001. A Separate Disease Within the Syndrome of Schizophrenia. Arch Gen Psychiatry 58, 165–171. https://doi.org/10.1001/ARCHPSYC.58.2.165.

Larabi, D.I., Gell, M., Amico, E., Eickhoff, S.B., Patil, K.R., 2022. Spatially localized fMRI metrics as predictive and highly distinct state-independent fingerprints. bioRxiv 2021.08.03.454862. 10.1101/2021.08.03.454862.

Laumann, T.O., Gordon, E.M., Adeyemo, B., Snyder, A.Z., Joo, S.J., Chen, M.-Y., Gilmore, A.W., McDermott, K.B., Nelson, S.M., Dosenbach, N.U.F., et al., 2015. Functional system and areal organization of a highly sampled individual human brain. Neuron 87, 657–670.

Lecrubier, Y., Sheehan, D. v., Weiller, E., Amorim, P., Bonora, I., Sheehan, K.H., Janavs, J., Dunbar, G.C., 1997. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. European Psychiatry 12, 224–231. 10.1016/S0924-9338(97)83296-8.

Leucht, S., Kane, J.M., Kissling, W., Hamann, J., Etschel, E., Engel, R.R., 2005. What does the PANSS mean? Schizophr Res 79, 231–238. https://doi.org/10.1016/j.schres.2005.04.008.

Leucht, S., Samara, M., Heres, S., Davis, J.M., 2016. Dose Equivalents for Antipsychotic Drugs: The DDD Method. Schizophr Bull 42, S90. https://doi.org/10.1093/SCHBUL/SBV167.

Liu, J., Liao, X., Xia, M., He, Y., 2018. Chronnectome fingerprinting: identifying individuals and predicting higher cognitive functions using dynamic brain connectivity patterns. Hum Brain Mapp 39, 902–915.

Matlab, 2021. Version: 9.11.0.1769968 (R2021b). The MathWorks Inc., Natick, Massachusetts.

Mueller, S., Wang, D., Fox, M.D., Yeo, B.T.T., Sepulcre, J., Sabuncu, M.R., Shafee, R., Lu, J., Liu, H., 2013. Individual variability in functional connectivity architecture of the human brain. Neuron 77, 586–595. https://doi.org/10.1016/J.NEURON.2012.12.028.

Ousdal, O.T., Kaufmann, T., Kolskår, K., Vik, A., Wehling, E., Lundervold, A.J., Lundervold, A., Westlye, L.T., 2020. Longitudinal stability of the brain functional connectome is associated with episodic memory performance in aging. Hum Brain Mapp 41, 697–709. https://doi.org/10.1002/hbm.24833.

Poldrack, R.A., Laumann, T.O., Koyejo, O., Gregory, B., Hover, A., Chen, M.Y., Gorgolewski, K.J., Luci, J., Joo, S.J., Boyd, R.L., Hunicke-Smith, S., Simpson, Z.B., Caven, T., Sochat, V., Shine, J.M., Gordon, E., Snyder, A.Z., Adeyemo, B., Petersen, S.E., Glahn, D.C., Mckay, D.R., Curran, J.E., Göring, H.H.H., Carless, M.A., Blangero, J., Dougherty, R., Leemans, A., Handwerker, D.A., Frick, L., Marcotte, E.M., Mumford, J.A., 2015. Long-term neural and physiological phenotyping of a single human. Nature Communications 2015 6:1 6, 1–15. 10.1038/ncomms9885.

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064.

Ritchie, S.J., Cox, S.R., Shen, X., Lombardo, M. v., Reus, L.M., Alloza, C., Harris, M.A., Alderson, H.L., Hunter, S., Neilson, E., Liewald, D.C.M., Auyeung, B., Whalley, H.C., Lawrie, S.M., Gale, C.R., Bastin, M.E., McIntosh, A.M., Deary, I.J., 2018. Sex Differences in the Adult Human Brain: Evidence from 5216 UK Biobank Participants. Cerebral Cortex 28, 2959–2975. 10.1093/CERCOR/BHY109.

Rolls, E.T., Loh, M., Deco, G., Winterer, G., 2008. Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. Nature Reviews Neuroscience 2008 9:9 9, 696–709. 10.1038/nrn2462.

Santo-Angles, A., Salvador, R., Gomar, J.J., Guerrero-Pedraza, A., Ramiro, N., Tristany, J., Teixidó, C., Ortiz-Gil, J., Aguirre, C., Bosque, C., López-Araquistain, L., Maristany, T., Salgado-Pineda, P., Sarró, S., McKenna, P.J., Bernardo, M., Pomarol-Clotet, E., Schwarzbach, J., 2021. Interindividual variability of functional connectome in schizophrenia. Schizophr Res 235, 65–73. https://doi.org/10.1016/J.SCHRES.2021.07.010.

Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2018. Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. Cerebral Cortex 28, 3095–3114. https://doi.org/10.1093/CERCOR/BHX179.

Sheehan, D. v., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59, 20–33.

Shen, X., Finn, E.S., Scheinost, D., Rosenberg, M.D., Chun, M.M., Papademetris, X., Constable, R.T., 2017. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. Nature Protocols 2017 12:3 12, 506–518. 10.1038/nprot.2016.178.

Sokunbi, M.O., Gradin, V.B., Waiter, G.D., Cameron, G.G., Ahearn, T.S., Murray, A.D., Steele, D.J., Staff, R.T., 2014. Nonlinear Complexity Analysis of Brain fMRI Signals in Schizophrenia. PLoS One 9, e95146.

Svaldi, D.O., Goñi, J., Abbas, K., Amico, E., Clark, D.G., Muralidharan, C., Dzemidzic, M., West, J.D., Risacher, S.L., Saykin, A.J., Apostolova, L.G., 2021. Optimizing differential identifiability improves connectome predictive modeling of cognitive deficits from functional connectivity in Alzheimer's disease. Hum Brain Mapp 42, 3500–3516. https://doi.org/10.1002/HBM.25448.

Talpalaru, A., Bhagwat, N., Devenyi, G.A., Lepage, M., Chakravarty, M.M., 2019. Identifying schizophrenia subgroups using clustering and supervised learning. Schizophr Res 214, 51–59. https://doi.org/10.1016/J.SCHRES.2019.05.044.

Tepper, Á., Cuiza, A., Alliende, L.M., Mena, C., Ramirez-Mahaluf, J.P., Iruretagoyena, B., Ornstein, C., Fritsch, R., Nachar, R., González-Valderrama, A., Undurraga, J., Cruz, J.P., Tejos, C., Fornito, A., Repetto, G., Crossley, N., 2022. Functional Dysconnectivity in Ventral Striatocortical Systems in 22q11.2 Deletion Syndrome. Schizophr Bull 48, 485–494. https://doi.org/10.1093/SCHBUL.SBAB139.

Tian, Y., Margulies, D.S., Breakspear, M., Zalesky, A., 2020. Topographic organization of the human subcortex unveiled with functional connectivity gradients. Nature Neuroscience 2020 23:11 23, 1421–1432. 10.1038/s41593-020-00711-6.

Undurraga, J., Negussie, H., Wendler, D., 2022. Consent, decisional capacity and guardianship in mental health research. Wellcome Open Research 2022 7:183 7, 183. 10.12688/wellcomeopenres.18003.1.

van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychol Rev 24, 32–48. https://doi.org/10.1007/s11065-014-9248-7.

Wong, A.H.C., van Tol, H.H.M., 2003. Schizophrenia: from phenomenology to neurobiology. Neurosci Biobehav Rev 27, 269–306. https://doi.org/10.1016/S0149-7634(03)00035-6.

Yeo, B.T.T., Krienen, F.M., Chee, M.W.L., Buckner, R.L., 2014. Estimates of segregation and overlap of functional connectivity networks in the human cerebral cortex. Neuroimage 88, 212–227. https://doi.org/10.1016/J.NEUROIMAGE.2013.10.046.

Zilles, K., Amunts, K., 2013. Individual variability is not noise. Trends Cogn Sci 17, 153–155. https://doi.org/10.1016/J.TICS.2013.02.003.