Distinct signatures of OSSOs compared to SSDs and HC using graph theory analysis

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Objectives

No studies have explored the differences in topological properties of resting-state fMRI (rs-fMRI) between patients with Other Specified Schizophrenia Spectrum and Other Psychotic Disorders (OSSOs) and Schizophrenia Spectrum Disorders (SSDs). This study aimed to investigate these differences in functional brain connectomes using a graph theory approach.

Methods

We recruited 86 OSSOs, 77 SSDs, and 83 healthy controls (HC) matched for age, sex, and education. OSSOs were further divided into subgroups: those with stable diagnoses for over one year (OSSOs ≥1-year) and those with pure delusion (PD). Global and local network metrics were obtained via graph-based rs-fMRI analysis, with Network-Based Statistic (NBS) performed as ancillary analysis.

Results

For local metrics, OSSOs had significantly higher betweenness centrality in the right thalamus than SSDs and HC, while SSDs showed increased betweenness centrality in the right thalamus compared to HC. Although the betweenness centrality of the right thalamus was significantly higher in PD than in SSDs and HC, SSDs demonstrated a higher nodal clustering coefficient in the left middle temporal gyrus compared to OSSOs ≥1-year and HC (Fig.1).

Both OSSOs and SSDs showed intact global network properties but exhibited higher global functional connectivity strength and hyperconnectivity within an interconnected component compared to HC (Fig. 2). Subgroup analysis showed that PD, OSSOs ≥1-year, and SSDs maintained intact global metrics but exhibited higher global functional connectivity strength and hyperconnectivity relative to HC (Fig.3 and Fig.4).

Table 1. Demographic and clinical characteristics of SSDs, OSSOs and HC

Characteristics	SSDs (n = 77)	OSSOs (n = 86)	PD (n = 51)	OSSOs≥1-year (n = 47)	HC (n = 83)	p-value Main	Sub-1	Sub-2
Age (years)	34.51 (10.04)	33.72 (11.00)	34.35 (9.96)	33.51 (11.06)	33.19 (8.54)	0.706ª	0.645ª	0.686ª
Sex								0.817ᵇ
Male (%)	39 (50.65)	43 (50.00)	24 (47.06)	22 (46.81)	38 (45.78)	0.796ᵇ	0.820ᵇ	
Female (%)	38 (49.35)	43 (50.00)	27 (52.94)	25 (53.19)	45 (54.22)			
Education (years)	13.77 (2.21)	14.04 (2.21)	14.39 (1.96)	13.66 (2.61)	13.42 (1.77)	0.157ª	0.031ª	0.545ª
Age of onset (years)	28.30 (9.84)	26.56 (8.77)	26.72 (8.40)	26.79 (9.57)	–	0.237ª	0.396ª	0.407ª
DI (months)	75.49(85.50)	82.08 (91.12)	99.31 (95.10)	85.12 (14.90)	–	0.097ª	0.291ª	0.264ª
Min	0.75	0.1	0.56	0.25	–			
Max	420	384	384	384	–			
PANSS								
Positive symptoms	18.10 (6.37)	12.44 (5.99)	13.29 (5.15)	11.87 (4.88)	–	<0.001ª	<0.001ª	<0.001ª
Negative symptoms	9.56 (2.55)	9.99 (3.52)	10.31 (3.77)	10.23 (3.53)	–	0.379ª	0.169ª	0.223ª
General psychopathology	27.53 (6.73)	25.49 (6.06)	25.75 (6.62)	25.15 (5.67)	–	0.044ª	0.071ª	0.046ª
Total	55.19 (13.46)	47.92 (12.35)	47.98 (13.38)	47.26 (11.92)	–	<0.001ª	0.005ª	0.001ª
Medication								
Drug naïve (%)	15 (19.48)	9 (10.47)	3 (5.88)	3 (6.38)	–			
Drug free (%)	12 (15.58)	27 (31.40)	19 (37.25)	17 (36.17)	–			
CPZ equivalent	425.68 (290.14)	294.55 (318.31)	334.94 (390.96)	345.17 (389.06)	–	0.034ª	0.243ª	0.303ª

SSDs vs OSSOs vs HC, SSDs vs PD vs HC, SSDs vs OSSOs≥1-year vs HC are labelled as Main, Sub-1, and Sub-2, respectively; Data means (± standard deviation), ªANOVA, analysis of variance; ᵇSignificant F statistic for the Chi-square test; ᶜSignificant T statistic for the two-sample t-test
Note: CPZ, Chlorpromazine equivalents/day, DI, Duration of illness; HC, Healthy controls, OSSOs, Other Specified Schizophrenia Spectrum and Other Psychotic Disorders; OSSO≥1-year, Other Specified Schizophrenia Spectrum and Other Psychotic Disorders (Diagnosis stability ≥ 1 year); PANSS, Positive and Negative Syndrome Scale; PD, Pure delusion; SSDs, Schizophrenia Spectrum Disorders.

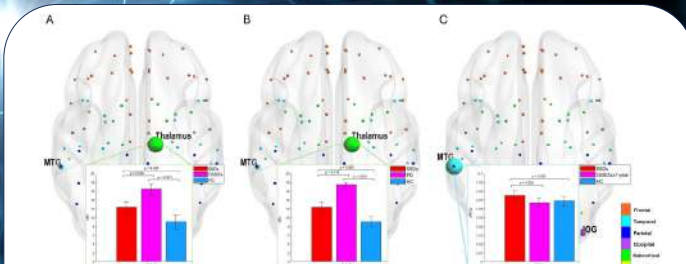**Fig. 1. Local metrics: (A)** Comparison of betweenness centrality among the SSDs, and OSSOs and HC; **(B)** Comparison of betweenness centrality among the SSDs, and PD and HC; and **(C)** Comparison of nodal clustering coefficient among the SSDs, and OSSOs≥1-year and HC. We used ANCOVA, adjusting for age and sex, with FDR correction applied.
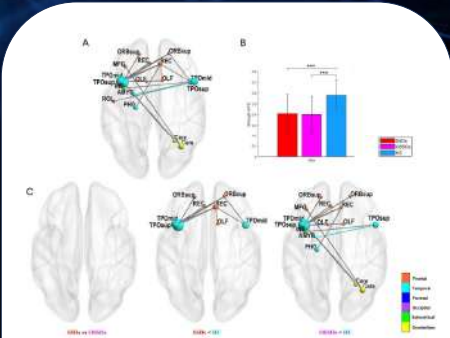

Fig. 2. NBS analysis: (A) Altered connectomes among three main groups: Using one-way ANCOVA (age and sex) with 10000 permutations (p<0.01 and F=8.6). Significant different (p=0.0097) a connected component was detected (19 edges between 17 nodes) among SSDs, OSSOs, and HC. In the post-hoc tests, No significant result between the OSSOs and SSDs. SSDs had significantly lower FC with a connected component than HC. OSSOs had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 8 edges between 9 nodes). OSSOs had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 14 edges between 15 nodes); **(B)** Strength of FC in altered a connected component; and **(C)** Brain map visualisation of the altered a connected component.
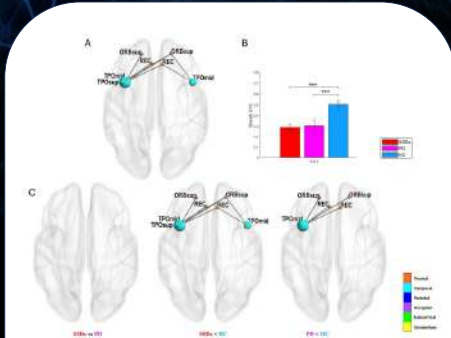

Fig. 3. NBS analysis: (A) Altered connectomes among three subgroups: Using one-way ANCOVA (age and sex) with 10000 permutations (p<0.01 and F=10). Significant different (p=0.0081) a connected component was detected (7 edges between 7 nodes) among SSDs, PD, and HC. In the post-hoc tests, No significant result between the PD and SSDs. SSDs had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 7 edges between 7 nodes). PD had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 4 edges between 5 nodes); **(B)** Strength of FC in altered a connected component; and **(C)** Brain map visualisation of the altered a connected component.
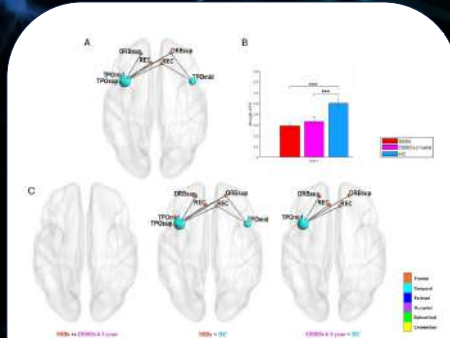

Fig. 4. NBS analysis: (A) Altered connectomes among three subgroups: Using one-way ANCOVA (age and sex) with 10000 permutations (p<0.01 and F=10). Significant different (p=0.0087) a connected component was detected (7 edges between 7 nodes) among SSDs, OSSOs≥1-year, and HC. In the post-hoc tests, No significant result between the OSSOs≥1-year and SSDs. SSDs had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 7 edges between 7 nodes). OSSOs≥1-year had significantly lower FC with a connected component than HC. CC1 (p<0.0001, 4 edges between 5 nodes); **(B)** Strength of FC in altered a connected component; and **(C)** Brain map visualisation of the altered a connected component.

Conclusion

These findings indicate potential network biomarkers for differentiating OSSOs from SSDs. Additionally, they may support the hypothesis that OSSOs should be regarded as a distinct clinical syndrome with a unique neural network.

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