Structural connectivity and rich-club organization in recent onset psychosis

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Dear Editors,

Studying psychosis in its early stages is important to better understand illness progression and any associated neuroanatomical change. Growing evidence suggests that abnormal structural connectivity may represent a biological marker of psychosis, with altered organization reported both at a prodromal and an early stage of the disorder (Schmidt et al., 2016; Zhang et al., 2015). Through the implementation of a graph theoretical approach, it is possible to investigate in detail how specific brain regions are integrated, segregated or central in the whole-brain structural network (Sporns, 2012). We addressed local graph topological properties in a number of regions previously found to be implicated in early psychosis (Ellison-Wright et al.,2008) in order to clarify the collective role of such nodes in patients at an early stage of the disorder, approximately three years after their first psychotic episode. Furthermore, we investigated the organization of rich-club structures, consisting of highly central and densely interconnected regions considered to have a key role in interregional brain communication and integration (van den Heuvel & Sporns, 2011).

Diffusion tensor imaging (DTI) datasets employing the identical acquisition parameters as per O'Donoghue et al. (2017) were obtained from 26 patients with recent onset psychosis (ROP; 17 males, mean age 31.9, SD=9), who were scanned approximately 3 years after their first presentation, and 26 healthy controls (HC; 15 males, mean age 37.9, SD=9). Participants' recruitment and more detailed clinical characteristics are outlined in Kenney et al. (2015). Network graphs were weighted by number of streamlines (NOS), fractional anisotropy (FA) and rich-club coefficients derived as outlined previously (O'Donoghue et al., 2017)

The two groups were gender matched, but significantly differed for age ($t=2.335$, $p=0.024$), with ROP being younger than HC. Symptoms severity in patients was assessed using the Positive and Negative Syndrome Scale (PANSS, total=43±13). MANCOVA tests, covaried for age and gender, were performed across groups for local graph metrics in a priori selected nodes of interest. Results are outlined in table 1. Specifically, two nodes of interest presented significant connectivity differences that survived multiple comparison correction, in NOS but not FA-weighted networks. The left amygdala revealed an increased clustering coefficient in ROP compared to HC, whereas the left anterior cingulate (ACG) presented a decrease in betweeness centrality in patients. An increase in

the clustering coefficient of the left amygdala that did not survive multiple comparison correction was evident also in FA-weighted networks.

Both groups presented a rich-club organization, with normalized weighted rich club coefficient (Φw_{norm}) > 1. However, the rich-club organization in ROP revealed subtle abnormalities in patients, with the right thalamus missing and the left middle occipital gyrus (MOG) additionally recruited relative to healthy controls. The rich clubs organization of both groups otherwise involved bilateral caudate, hippocampus, putamen, precuneus, and the left thalamus.

Applying this novel network analysis, we identified local brain topology abnormalities early in the course of psychosis, particularly affecting the limbic system. This is consistent with the regional pattern of deficits previously reported in the early stages of schizophrenia (Ellison-Wright et al., 2008). Disrupted integration of the ACG in ROP might lead to aberrant emotional and cognitive preprocessing, whereas an increase in the efficiency and integration of the amygdala may reflect an overactive response to emotional stimuli in psychosis. Furthermore, the subtle anomalies found the rich-club organization in psychotic patients might represent deficits in global brain communication already present at this stage of the disorder. Importantly, the thalamus is a key hub in global communication, and its disrupted connectivity could contribute to broader symptomatology and will be important to investigate in future studies. In contrast, the involvement of the MOG in the rich-club structure has been recently reported in bipolar patients (O'Donoghue et al., 2017), potentially representing a compensatory effect from early integration impairments.

It is important to highlight that our cohort comprises patients who experienced their first psychotic episode 3 years prior to scanning, with variable levels of recovery, and most were taking psychotropic medications. These factors, together with the clinical heterogeneity of our sample, consisting of patients with affective and non-affective psychosis, might have obscured our ability to detect topological and global abnormalities specific to schizophrenia or bipolar disorder.

This structural connectivity analysis represents a promising approach for the characterization of dysconnectivity in psychosis. Taken together, our findings indicate the existence of subtle connectivity deficits at an early stage of the disorder, specifically involving limbic structures, which might represent trait features for psychosis.

Table 1. Local connectivity differences between HC and ROP, covaried for age and gender.

Nodes		**Clustering coefficient F, p**		**Local Efficiency F, p**		**Betweenness Centrality F, p**	
		NOS-weighted	FA-weighted	NOS-weighted	FA-weighted	NOS-weighted	FA-weighted
Insula	Left	0.001, 0.980	0.207, 0.651	0.062, 0.805	0.335, 0.566	0.467, 0.498	0.004, 0.949
	Right	0.579, 0.450	0.115, 0.736	0.311, 0.580	0.040, 0.843	1.101, 0.300	3.638, 0.063
Anterior Cingulate	Left	0.365, 0.566	0.089, 0.766	0.094, 0.761	0.242, 0.625	10.609, 0.002**	2.633, 0.112
	Right	2.026, 0.161	0.349, 0.557	1.872, 0.178	0.278, 0.601	0.222, 0.640	0.017, 0.898
Amygdala	Left	11.040, 0.002**	4.127, 0.048*	9.122, 0.004*	3.080, .086	2.567, 0.116	1.908, 0.174
	Right	2.017, 0.162	0.006, 0.937	0.488, 0.488	0.313, 0.578	4.443, 0.041*	0.094, 0.760
Postcentral gyrus	Left	0.460, 0.501	0.000, 0.983	0.476, 0.493	0.019, 0.891	5.840, 0.020*	0.539, 0.466
	Right	0.338, 0.564	0.486, 0.489	0.103, 0.750	0.409, 0.526	0.000, 0.991	2.831, 0.099
Supramarginal gyrus	Left	0.138, 0.712	0.005, 0.944	0.062, 0.805	0.250, 0.620	1.513, 0.225	1.154, 0.289
	Right	1.452, 0.234	4.427, 0.041*	1.898, 0.175	1.604, 0.211	1.724, 0.197	0.977, 0.329
Putamen	Left	0.614, 0.437	0.186, 0.668	1.669, 0.203	0.109, 0.742	0.255, 0.616	0.104, 0.748
	Right	3.647, 0.062	0.560, 0.458	3.834, 0.056	0.107, 0.745	0.642, 0.427	0.255, 0.616
Thalamus	Left	0.020, 0.887	0.102, 0.751	0.364, 0.549	0.221, 0.640	2.181, 0.146	0.013, 0.909
	Right	1.499, 0.227	1.101, 0.299	2.102, 0.154	0.172, 0.680	0.229, 0.634	0.011, 0.917
Caudate	Left	1.382, 0.246	0.070, 0.792	2.107, 0.153	0.005, 0.946	0.394, 0.533	0.380, 0.540
	Right	1.619, 0.209	0.921, 0.342	1.393, 0.153	0.255, 0.616	2.417, 0.126	0.039, 0.843

* Significant differences that did not survive FDR correction; ** Significant differences that survived FDR correction.

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