# Diffusion spectrum imaging connectomics: a biomarker for staging in psychotic disorders

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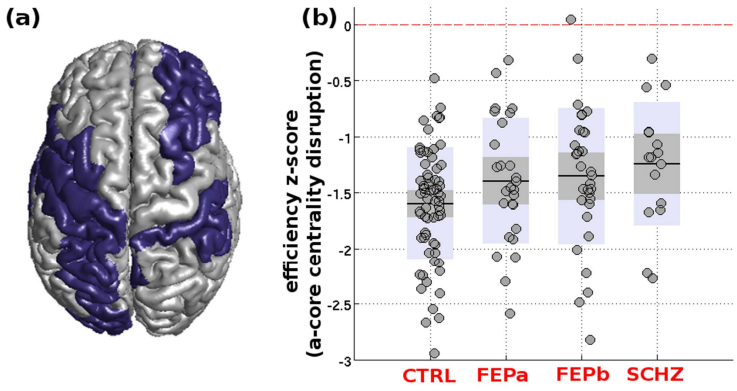
Target audience: Researchers and clinicians interested in psychosis investigation, clinical staging, brain network analysis, connectomics.

Purpose: Schizophrenia is a severe psychiatric disorder hypothesized to result from brain connectivity impairment[1]. Precocious brain alterations can already be highlighted in the early stages of the pathology[2]. According to the concept of clinical staging in psychotic disorders, brain connectivity might by more abnormal in more severe stages of the pathology, and altered connectivity measures might show progressive changes from prodromal to chronic phase[3]. In a recent diffusion-based analysis on 16 chronic schizophrenia patients and 15 healthy controls, we identified a spatially distributed set of brain regions, dubbed affected core or a-core, driving the loss of global brain network properties[4]. Investigating a cohort of 59 early psychosis patients, in the present study we question: (i) whether alterations of global brain network properties are already present in the early stage of the disease, and (ii) whether the a-core is precociously affected in the disease. We propose affected core network measures as possible markers of illness progression.

Methods: 59 first episode psychosis patients having met the threshold for psychosis according to the CAARMS criteria[5] (FEP, 42M/17F, 26+/-6yo), and 59 age and gender matched healthy controls (CTRL, 40M/19F, 26+/-6yo) underwent an MRI session composed by MPRAGE and diffusion spectrum imaging (DSI) sequences. Moreover, 16 chronic schizophrenia patients (SCHZ, 10M/6F, 26+/-6yo) and 15 age and gender matched healthy controls (CTRL, 8M/7F, 41+/-9yo) underwent the same MRI, as reported in[4]. For FEP patients, the number of hospitalizations before the MRI scan was recorded. Subject-wise structural connectivity matrices were generated combining MPRAGE segmentation into 82 cortical and subcortical regions, and DSI reconstruction and streamline tractography, according to[6]. Brain connectivity matrices were weighted by the relative streamline density as in[4]. Global and local integration and segregation network properties were quantified through classical graph measures, and particularly global efficiency, transitivity, nodal closeness centrality, and nodal local efficiency[7]. The affected core subnetwork was previously identified as driving the loss of global network properties in the cohort of 16 SCHZ patients and 15 CTRL, and includes 26 brain regions (figure (a))[4]. In the present study the a-core of CTRL, FEP and SCHZ subjects was characterized by the following measures: efficiency and transitivity computed within the a-core subnetwork; generalized fractional anisotropy (gFA) and inverse apparent diffusion coefficient (iADC) averaged over the a-core edges; a-core centrality within the overall brain network. As in[4], the a-core centrality was characterized by comparing targeted attack toward the a-core itself with repeated random attacks, and computing the efficiency z-score (a-core centrality disruption) after targeted attack relative to its reference distribution[4]. Non-parametric Mann–Whitney U test (MWU, $\alpha$=0.05) was used for group comparison. Multiple comparison correction was applied when necessary (FDR=0.05). A generalized linear model (GLM) was used to assess the relationship between a-core measures and illness stages, i.e. early psychosis patients to chronic schizophrenia stages, while controlling by age and gender.




Results: Global network efficiency and transitivity, quantifying brain segregation and integration properties, were not affected in FEP patients compared to CTRL, as opposed to SCHZ patients[4]. None of the 82 brain regions' between-group comparison of nodal closeness centrality and local efficiency survived multiple comparison correction when comparing FEP and CTRL subjects. In order to assess affected core impairment in the early stage of psychosis, a-core measures were compared between FEP and CTRL subjects. Similarly to the SCHZ patients[4], efficiency and transitivity computed within the a-core were reduced in FEP compared to CTRL ($p<0.01$, $p<0.04$). The efficiency z-score (a-core centrality) was tendentially diminished in FEP ($p=0.07$). GFA ($p<0.003$) and iADC ($p<0.005$) were decreased in FEP compared to CTRL when averaged over the a-core connecting tracts, indicating an early impairment of the a-core regions. GLMs including CTRL subjects, FEP, and SCHZ patients, and covariates age and gender, highlighted a statistically significant dependency between a-core measures (a-core efficiency, transitivity, gFA, iADC and efficiency z-score) and type 1:CTRL/2:FEP/3:SCHZ ($0.00004<p<0.05$). Finally, FEP patients where subdivided into two sub-groups on the basis of the incidence of hospitalizations prior to the MRI scan: FEP subjects with 0 or 1 hospitalization (FEPa) and FEP with more than 1 hospitalization (FEPb). A-core efficiency and transitivity were significantly decreased in FEPb patients compared to CTRL ($p<0.004$, $p<0.04$), but between-group difference did not reach statistical significance when comparing FEPa patients and CTRL. A-core centrality, gFA and iADC were more consistently altered in FEPb than in FEPa compared to CTRL (lower p-values). Dispersion of efficiency z-score values for the four groups are reported in figure (b) (note that no statistical relationship between efficiency z-score and age and gender was found when considering the subject groups together or separately in a GLM). If we consider the hospitalizations incidence as possible indicator of illness severity, this result support the a-core measures as possible biomarkers of psychosis progression.

Discussion: Staging in psychotic disorders is clinically relevant for tailoring particular care to the severity of the disease. Importantly, neuroimaging techniques such as diffusion imaging, associated with advanced analysis tools such as graph theory, may help identifying biomarkers of illness progression, or characterizing specific stages of illness[3]. In this study we showed that global network properties, impaired in chronic schizophrenia, are not altered in the early stage of psychosis. Nonetheless, a distributed set of brain regions (a-core) extensively affected in chronic schizophrenia, is precociously impaired in the early stages of the disease. A GLM investigating a-core measures across the different psychosis stages suggests that a progressive impairment of the a-core brain subnetwork may worsen in time, eventually leading to a global brain efficiency loss not yet traceable in the earlier stages of the disease (b). Moreover the a-core subnetwork is more impaired in FEP patients presenting an higher number of hospitalizations before MRI.

Conclusion: This study investigates psychosis progression with a neuroimaging and graph theory perspective. A distributed set of brain regions (a-core) affected in the chronic stage of the disease is precociously impaired in the early stages. We propose a-core network measures as possible markers of illness progression, while loss of global network efficiency and transitivity might characterize the advanced stages of the disease.

References: 1.VanDenHeuvel M, Fornito A. Brain networks in schizophrenia. Neuropsychol Rev 2014;24:32-48. 2.Canu E et al. A selective review of structural connectivity abnormalities of schizophrenia patients at different stages of disease. Schizophr Res 2014;*InPress*. 3.Wood SJ et al. Neuroimaging and treatment evidence for clinical staging in psychotic disorders. Biol Psychiatry 2011;70:619-625. 4.Griffa A et al. Characterizing the connectome in schizophrenia with diffusion spectrum imaging. Hum Brain Mapp 2014;*In Press*. 5. Yung AR et al. Mapping the onset of psychosis. Aust N Z J Psychiatry 2005;39(11-12):964-971. 6.Hagmann P et al. Mapping the structural core of the human cerebral cortex. PloS Biol 2008;6(7):e159. 7.Rubinov M, Sporns O. Complex brain network measures of brain connectivity. Neuroimage 2010;52(3):059-1069.