Supplementary Information

Connectomic correlates of response to treatment in first-episode psychosis


* shared first authorship.

Contents

- Supplementary Methods
  - Subjects recruited
  - Regions of interest used
  - General linear model analysis
  - Network-based statistics

- Supplementary Figures
  - Supplementary Fig. 1: Streamline density in healthy controls, patients at baseline, and patients at follow-up.
  - Supplementary Fig. 2: Global efficiency in healthy controls, patients at baseline, and patients at follow-up.

- Supplementary Tables
  - Supplementary Table 1. Characteristics of patients scanned at 12 weeks and those that were not.
  - Supplementary Table 2. Characteristics of patients who responded to treatment and those that did not.
Supplementary Methods

Subjects recruited

Patients

Patients were recruited from psychiatric services of South London and Maudsley NHS Foundation Trust in London, United Kingdom. Clinical diagnoses were formulated using OPCRIT+ (McGuffin et al., 1991) and psychotic symptoms were evaluated at baseline on the day of MRI, and again after 12-weeks, using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). As described previously (Reis Marques et al., 2014), for those patients that did not return for follow-up assessment, information on treatment response was obtained using the World Health Organization (WHO) Personal and Psychiatric History Schedule (PPHS) (Jablensky et al., 1992) which showed substantial agreement with PANSS score criteria (kappa = 0.72). Therefore, all patients assessed at baseline were classified according to their subsequent response.

Duration of untreated psychosis was defined as the interval between the first appearance of psychotic symptoms and the first contact with psychiatric services. Dose of cumulative medication received in the 12-week period was calculated using chlorpromazine equivalents (Woods, 2003).

Controls

Healthy controls were screened for the presence of psychotic symptoms using the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995), with the family history of psychotic illness being screened during a clinical interview.

Regions of interest used

As has been previously noted, connectivity in DTI studies is not independent from the size of the regions of interest (ROIs), with a higher number of streamlines finishing in larger regions (van den Heuvel et al., 2013). In order to avoid this problem, we used a template of 401 similarly-sized regions built from subdivision of the regions from the Anatomical Automated Labeling Atlas (Tzourio-Mazoyer et al., 2002) using a modification of a validated algorithm (Zalesky et al., 2010). As such, regions
respected anatomical landmarks. We also subdivided first the gray/white matter interface where DTI tracts are likely to terminate. This implied that no subregions created would be entirely superficial and less likely to contact streamlines.

**General linear model analysis**

As described in the main text, we used a general linear model (GLM) framework to explore the role of being a patient, response to medication, changes over time, and the effect of medication. We first built a GLM to examine the baseline factors affecting the studied properties (streamline counts or graph analytic metrics), with a design matrix that we describe below:

\[ Y = \beta_0 + \beta_1 (\text{case}) + \beta_2 (\text{response}) + \beta_3 (\text{affective}) + \beta_4 (\text{age}) + \beta_5 (\text{gender}) + \beta_6 (\text{total streamlines}) + \varepsilon \]

When the baseline property assessed was total streamlines, the design matrix did not include this factor.

When examining the changes in follow-up, we modelled the difference between the studied metric (streamline counts or graph analytic metrics) between the two time points in patients using the following design matrix:

\[ Y = \beta_0 + \beta_1 (\text{response}) + \beta_2 (\text{affective}) + \beta_3 (\text{age}) + \beta_4 (\text{gender}) + \beta_5 (\text{total streamlines}) + \beta_6 (\text{medication}) + \varepsilon \]

**Network-based statistics**

We here used network-based statistics (Zalesky et al., 2010) as a way to find anatomically networks of connected regions modulated by one of our factors of interest. We used this method as a way to avoid multiple comparisons, capitalizing on the information obtained from the spatial clustering of the abnormalities (i.e. real effects are more likely to cluster spatially than false positives).

Our statistical test was based on the linear model described above, which explored how being a patient, responding to medication, or the dose of medication explained the number of streamlines in each edge, or the change in streamlines at follow-up. We
also included the covariates of no interest in our model, such as age, gender, or a clinical presentation with affective symptoms. In order to avoid connection differences being driven by variation in the size of brain regions across subjects, we also included in the model the sum of the volumes (in native space) of the regions connected by the edge.

We were interested in clustered reductions or increases in streamline numbers, and therefore looked for connected groups of regions in which all the links were being modulated by a specific factor in the same direction. For example, when exploring the effect of future response in connections, we would first look for networks where future non-response was related to decreases in their streamlines, and then, independently, with increases. We thus built two binary graphs representing either clustered increases or decreases for each of the variables explored in this manuscript, which were analyzed independently. To draw an edge in these graphs two conditions had to be fulfilled: 1) the streamline difference between groups attributed to that specific factor was in the direction explored (decreases or increases); and 2) the P value for the respective factor in the linear model was below a k factor of 0.005. The number of significant edges forming the biggest connected component in each graph was then compared to a null distribution built from 10,000 random permutations of the respective variable (i.e., patient or control, response, or follow-up). All P-values reported correspond to two-tailed comparisons.
Supplementary Figures

Supplementary Figure 1

**Streamline Density**

Supplementary Fig. 1. Streamline density in healthy controls, patients at baseline, and patients at follow-up. Connecting lines highlight the baseline and follow-up scan for the same subject.
Supplementary Figure 2

Supplementary Fig. 2. Global efficiency in healthy controls, patients at baseline, and patients at follow-up. Connecting lines highlight the baseline and follow-up scan for the same subject. Note that streamline density was already regressed out of the global efficiency parameter shown.
**Supplementary Table**

**Supplementary Table 1**

Characteristics of patients scanned at 12 weeks and those that were not.

<table>
<thead>
<tr>
<th></th>
<th>Patients scanned at baseline and follow-up</th>
<th>Patients scanned at baseline only</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>43</td>
<td>33</td>
<td>N.A</td>
</tr>
<tr>
<td>Age at baseline (mean (SD))</td>
<td>28.9 (7.8)</td>
<td>27.1 (9.3)</td>
<td>( P = 0.36 ) (t-test)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>25.6</td>
<td>36.3</td>
<td>( P = 0.31 ) (( \chi^2 ) 1.03, d.f. 1)</td>
</tr>
<tr>
<td>Education (% incomplete, completed school, further education)</td>
<td>9.3</td>
<td>9.1</td>
<td>( P = 0.37 ) (( \chi^2 ) 2.01, d.f. 2)</td>
</tr>
<tr>
<td>Total PANSS baseline (SD)</td>
<td>58.8 (14.1)</td>
<td>57.8 (13.8)</td>
<td>( P = 0.78 ) (t-test)</td>
</tr>
<tr>
<td>Duration of untreated psychosis (median days, inter-quartile range)</td>
<td>46.5 (20 - 180)</td>
<td>79.5 (14-552)</td>
<td>( P = 0.5 ) (Wilcoxon rank-sum test)</td>
</tr>
<tr>
<td>Cumulative antipsychotic dose received at baseline (mean Chlorpromazine equivalents, SD)</td>
<td>11035 (14601)</td>
<td>7027 (8832)</td>
<td>( P = 0.24 ) (t-test)</td>
</tr>
<tr>
<td>Presence of affective symptoms (%)</td>
<td>41.9</td>
<td>42.4</td>
<td>( P = 0.96 ) (( \chi^2 ) 0.002, d.f. 1)</td>
</tr>
<tr>
<td>Response to antipsychotic (%)</td>
<td>46.5</td>
<td>39.3</td>
<td>( P = 0.53 ) (( \chi^2 ) 0.39, d.f. 1)</td>
</tr>
</tbody>
</table>

N.A= not applicable; S.D= standard deviation; d.f= degrees of freedom.
**Supplementary Table 2**  
**Characteristics of responders to treatment and those that did not**

<table>
<thead>
<tr>
<th></th>
<th>Patients who responded</th>
<th>Patients who did not respond</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>33</td>
<td>43</td>
<td>N.A</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>28.4 (8.3)</td>
<td>27.9 (8.7)</td>
<td>$P = 0.82$ (t-test)</td>
</tr>
<tr>
<td>(mean (SD) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (%)</td>
<td>39.4%</td>
<td>30.2%</td>
<td>$P = 0.40$ ($\chi^2 0.696$, d.f. 1)</td>
</tr>
<tr>
<td>(% female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (%)</td>
<td>3.0 39.4 57.6</td>
<td>14.0 55.8 30.2</td>
<td>$P = 0.034$ ($\chi^2 6.77$, d.f. 2)</td>
</tr>
<tr>
<td>(% incomplete, completed school, further education)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of untreated psychosis (median days, inter-quartile range)</td>
<td>42 (9-147)</td>
<td>62 (31-357)</td>
<td>$P = 0.12$ (Wilcoxon rank-sum test)</td>
</tr>
<tr>
<td>Presence of affective symptoms (%)</td>
<td>48.5%</td>
<td>37.2%</td>
<td>$P = 0.32$ ($\chi^2 0.974$ d.f. 1)</td>
</tr>
<tr>
<td>NART Intelligence Quotient (mean (SD) )*</td>
<td>90.8 (10.8)</td>
<td>91.7 (10.9)</td>
<td>$P = 0.76$ (t-test)</td>
</tr>
</tbody>
</table>

N.A= not applicable; S.D= standard deviation; d.f= degrees of freedom; NART=National Adult Reading Test.

* Sample reported include 25 responders and 32 non-responders for whom data was available.
References


Supplementary Information - Crossley, Marques et al.

