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Symptom remission and brain cortical networks at first clinical presentation of psychosis: the OPTiMiSE study

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Abstract

Individuals with psychoses have brain alterations, particularly in frontal and temporal cortices, that may be particularly prominent, already at illness onset, in those more likely to have poorer symptom remission following treatment with the first antipsychotic. The identification of strong neuroanatomical markers of symptom remission could thus facilitate stratification and individualised treatment of patients with schizophrenia.

We used Magnetic Resonance Imaging (MRI) at baseline to examine brain regional and network correlates of subsequent symptomatic remission in 167 medication-naïve or minimally treated patients with first episode schizophrenia, schizophreniform disorder, or schizoaffective disorder entering a three phase trial, at seven sites. Patients in remission at the end of each phase were randomized to treatment as usual, with or without an adjunctive psycho-social intervention for medication adherence. Final follow-up visit was at 74 weeks.

108 patients (70%) were in remission at Week-4, 85 (55%) at Week-22, and 97 (63%) at Week-74. We found no baseline regional differences in volumes, cortical thickness, surface area or local gyrification between patients who did or did not achieved remission at any time-point. However, patients not in remission at Week-74, at baseline showed reduced structural connectivity across frontal, anterior cingulate and insular cortices. A similar pattern was evident in patients not in remission at Week-4 and Week-22, although not significantly.

Lack of symptom remission in first episode psychosis is not associated with regional brain alterations at illness onset. Instead, when the illness becomes a stable entity, its association with altered organisation of cortical gyrification becomes more defined.

Keywords: Schizophrenia, MRI, gyrification, trial, first episode, cortical thickness, OPTIMISE

Introduction

The response to treatment in schizophrenia is heterogeneous. Although most patients achieve symptom remission with antipsychotic medication, around 30% do not respond to treatment. At present, there are no validated biomarkers that can be used to predict symptom remission, so the therapeutic response has to be determined empirically through clinical evaluation of a course of antipsychotic treatment. Although many first episode patients show symptomatic improvement after the first 2-4 weeks of treatment, others only improve after 10 weeks of treatment, and some of those who initially appeared to be in remission may later become symptomatic again[1]. This variability in the time to antipsychotic response, and the instability of remission status in the early phase of treatment has complicated the identification of its neurobiological correlates. These issues can be addressed by investigating the predictors of remission at multiple time points following the initiation of treatment.

At present, the relationship between brain morphometry at psychosis onset and remission following subsequent treatment is unclear. Previous studies have assessed remission mostly beyond the first year of illness and at varying illness stages. Moreover, they have used different criteria to define remission, have involved different durations of treatment, and have evaluated relatively modest sample sizes[2]. Collectively, these studies suggest that the predictors of later poorer outcomes include alterations in prefrontal and temporal volume, thickness and gyrification, and alterations in the networks that connect these regions with subcortical structures[3-5].

Only a handful of studies have investigated the brain structural correlates of symptom remission in the first six months of illness (for a review see[2]). Our previous work suggests that in first episode patients, cortical folding defects in frontotemporal regions and insula, altered integrity of white matter tracts connecting these regions, and a reconfiguration of gyrification networks are associated with later non-remission after 12 weeks of treatment[6, 7].

Other studies have found network differences in relation to subsequent treatment response at 24 weeks, but no regional differences[8]. The presence of network alterations in the absence of localized differences may reflect distributed changes that vary in location across subjects, and that may not be detected by voxel-based methods of analyses, hence the need for evaulations that go beyond morphometric measures.

In the present study we used Magnetic Resonance Imaging (MRI) to examine a large sample of medication-naïve or minimally-treated patients with first episode schizophrenia, schizophreniform or schizoaffective disorder who participated in a clinical trial of standardised antipsychotic treatments. We then evaluated the relationship between their baseline brain morphometric and network features and remission at the end of each treatment phase (4, 22 and 74 weeks). We tested the hypothesis that alterations in regional morphometry (reduced cortical thickness, surface area, and gyrification of frontal and temporal areas) and in network organisation would be associated with non-remission. We also explored whether a support vector machine analysis of the network data at baseline could be used to predict remission status.

Methods & Materials

Study Design and Participants

Patients with a first episode of schizophrenia, schizoaffective or schizophreniform disorder were included from the OPTiMiSE study, a multi-centre trial of antipsychotic medication[1] (www.optimisetrial.eu; EudraCT Number: 2010-020185-19; clinicaltrials.gov identifier: NCT01248195). Full details of the protocol and the primary clinical results have been published previously[1] (see Appendix in Supplementary Material for trial diagram). Seven of the trial sites, which comprised psychiatric inpatient and outpatient facilities, participated in the present MRI sub-study (Copenhagen, London, Madrid, Naples, Prague, Tel Aviv, Utrecht).

Participants were 18 year and older and met DSM-IV criteria for first episode schizophrenia, schizophreniform disorder or schizoaffective disorder confirmed by the Mini International Neuropsychiatric Interview plus. Exclusion criteria were: onset of psychotic symptoms >2 years prior to recruitment; supra-threshold antipsychotic medication use (>2 weeks in the preceding year, or >6 weeks lifetime); known intolerance to study drugs; meeting contra-indications for study drugs; coercively treated or under legal custody; pregnant or breastfeeding and meeting MRI contraindications. All study sites had local ethical and regulatory approval. Written informed consent was required for all participants.

We also included a reference sample of 113 healthy controls (see Table S3) with no history of psychiatric illness or MRI contraindications (mean age: 25.1, sd: 5.25; 37.2% female) for interpretation of results in the patient group.

Assessment, Treatment, and Treatment Response

At baseline, after screening, participants were assessed using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and underwent MRI scanning. They then

entered the first of up to three treatment phases. All participants started treatment with amisulpride (200–800 mg/day orally; phase I). After 4 weeks, the PANSS was administered again and used to determine whether patients were in remission. Symptom remission was defined using the modified symptom component of the Remission in Schizophrenia Working Group[9], which requires that PANSS symptom severity scores for 8 criterion items are ≤3. Patients who were not in remission at this stage were randomly assigned 1:1 to double-blind flexible dose treatment with either olanzapine (5−20 mg/day orally) or amisulpride (200−800 mg/day orally) for 6 weeks (Phase II). Patients who were not in remission at the end of Phase II continued into 12-week open-label treatment with oral clozapine (100−900 mg/day (Phase III). At the end of phases I, II and III patients who were in remission were randomized to continuing treatment, with or without an adjunctive psycho-social intervention designed to increase adherence to medication. The latter comprised web-based psychoeducation, motivational interviewing and mobile phone adherence management. Patients who had dropped out during any phase of the trial or who were not in remission at the end of Phase III were also randomized within this study component. Patients were assessed using the PANSS related to the previos week at weeks 1, 2, 4, 6, 8, and 10–22, across all trial treatment arms. For all patients who started Phase I, a follow-up visit to assess symptom severity and current clinical diagnosis was scheduled at 74 weeks post baseline, timed to be 1 year after the end of Phase III study medication.

For the purpose of the present MRI study, we considered whether patients were Remitted or Non-Remitted according to remission criteria evaluated at three time points: 1) at the end of first treatment (*Week-4 Remission*, determined using PANSS at 4-weeks as end of phase I); 2) at end of the pharmacological protocol (*Week-22 Remission*, determined at week 22 as end of Phase III, or with the closest last available PANSS, either from the main study or the psychosocial intervention arm); and 3) at the final follow up visit (*Week-74 Remission*, determined at week 74, or with the closest last available PANSS score, either from the main study or the psychosocial intervention arm).

Image Acquisition and processing

Details of the data acquisition protocol and image pre-processing for each site can be found in the Supplementary Material, eTable 1 and eTable 2. All images were screened for radiological abnormalities, and individuals with clinically significant findings (such as brain neoplasms) were excluded from further analysis (n=5 patients). After quality control, we employed Freesurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu/) for cortical and subcortical reconstruction, parcellation and estimation of regional morphometric measures.

Gyrification Covariance Networks

Network analysis can provide insight into structural connectivity at multiple levels, from pairwise connections between regions, up to the organisational properties of the whole network. Here, gyrification-based structural covariance networks were constructed for each treatment outcome group (remission and non-remission, at each time point) and for controls using the mean local gyrification index (LGI)[10] values of the 62 cortical regions of the Desikan-Killianny-Tourville (DKT) atlas (after adjustment for covariates; eTable S5). We selected this atlas as it uses robust sulcal landmarks and well reproduces manual labelling in a large sample[11]. Within each group pairwise Pearson's correlation coefficients between atlas regions (n=62 regions; 1,891 pairs) were calculated to construct a network of 1,891 connections. To efficiently combat the inherent multiple comparisons correction problem, we employed network-based statistic (NBS[12]) to identify affected network components (sub-networks of linked connections) which share the same supra-thresholded group effect. This approach is analogous to the common use of clusters in fMRI and VBM analysis, but clusters are defined from network connectivity rather than from spatial connectivity.

The broader impact on the organisation of the brain network was investigated using graph-theoretical measures in fixed connection-density, binarized networks. Such analysis of fixed density (also termed fixed wiring-cost) networks is appropriate for densely connected

networks (like those obtained from structural covariance) as it ensures that measures reflect the arrangement of connections in the network rather than simply the number or magnitude of the connections. A range of densities from 0.05 to 0.50 were assessed in steps of 0.05 and an overall estimate obtained by computing the area under the density curve (AUC). Global and local efficiency were analysed to assess group differences in the suitability of the LGI network for efficient overall communication (global) and robust/specialised regional communication (local). Further to this, node-wise eigenvector centrality was calculated as a measure of the relative importance/influence of individual nodes in the LGI network.

Statistical methods

Statistical analysis was conducted in R version 3.5.1 (https://www.R-project.org/) with Freesurfer mri_glmfit software for spatial cluster-based statistics on the cortical surface.

Analyses were adjusted for the following covariates: age, gender, and estimated total intracranial volume (linear effects), scanning site (modelled as a fixed effect). For the multivariate prediction models, and structural covariance networks analyses, residualisation for the effects of covariates was performed prior to analysis.

We conducted conventional mass-univariate testing to localise between-group differences in structural measures. For gyrification networks, significantly affected network components were determined using the Network-Based Statistic (NBS)[12]. Details of both univariate testing and gyrification network analyses are presented in the Supplementary Material.

In an additional analysis we also estimated prediction models for the regional Freesurfer data with linear-kernel Support Vector Machines to explore if these measures could be used to provide accurate individual predictions (see Supplementary Material for details).

Results

Of the 371 participants from the OPTiMiSE study who completed phase I, 167 underwent MRI scanning and 154 (mean age: 25.3, sd: 6.10; 34.4% female) of these were included in the analyses (after exclusions as detailed above), 64 (42%) of whom were drug-naïve. Patients who had an MRI had lower total PANSS scores at baseline (70.3 vs. 82.5, $p<0.001$) than patients who did not undergo scanning, but were otherwise similar (eTable 4).

Figure 1 shows a flow diagram of patient remission status at each time-point, and represents the proportion of patients that changed status over the three timepoints of assessments. By Week-4, 108 (70%) of the 154 patients met Remission criteria. At Week-22, 85 (55%) patients were in remission, and at Week-74, 97 (63%) patients were in remission. The last available PANSS observation data were used for 42 patients at Week 22 (with 29 Remitted at last observation) and for 62 patients at Week 74 (with 33 remitted at last observation). Table 1 displays the main demographic and clinical details for each sub-set, with additional clinical details shown in eTable 6. eTable 3 presents demographic and clinical charateristics across scanning sites.

[TABLE 1]

[FIGURE 1]

MRI Correlates of Remission

Freesurfer Analysis

There were no statistically significant differences between patients not in remission and those in remission at Week-4, Week-22 and at Week-74, for either cortical thickness, surface area, subcortical volume or LGI (all $p>0.05$, adjusted).

Gyrification Networks

Structural connectivity was markedly reduced in the patients Non-Remitted at Week-74 compared to the Remitted, across a distributed network. The edgewise analysis identified 12 connections which were each significant at $p<0.05$, FDR corrected. The NBS analysis put this in a wider context, identifying a single altered network component comprising 29 connections (permutation $p=0.049$, Table 2, Figures 3A, 3B). This network was centred on the left frontal cortex, anterior cingulate, and insular cortex. To probe the origins of these differences, we extracted the same 29 connections from the earlier Week-4 and Week-22 groupings and found that average structural connectivity of these connections was also reduced in the Non-Remitted relative to Remitted patients at both earlier time points, although the differences were not statistically significant (Figures 3C, 3D).

The analysis of fixed density network measures suggested that these effects were not strongly topological, as global and local efficiency measures were not significantly different between Remitted and Non-Remitted patients, even at Week-74 (Table 3). Similarly, there was no evidence of a substantial impact on nodal importance, as measured by eigenvector centrality (min FDR-corrected p-value=0.37). In the absence of correction for multiple comparisons, there was reduced centrality in Non-Remitted patients of the left rostral anterior cingulate cortex (ACC) (EVC: Remitted=0.213, Non-Remitted=0.034, $p=0.023$, uncorrected), and the left precentral region (EVC: Remitted=0.439, Non-Remitted=0.365, $p=0.04$, uncorrected), and an increase in eigenvector centrality in the Non-Remitted for the right inferior frontal gyrus pars triangularis region (i.e. contralateral to the affected network in Figure 3; EVC: Remitted=0.12, Non-Remitted=0.34, $p=0.006$, uncorrected). The regions with decreased centrality were seen in the NBS network (Table 2), particularly the left rostral ACC, which was the most commonly affected node, participating in 11 of 29 remission-related edges. This suggests that there is a regional effect detectable as reduced network importance for these nodes, although it seems to have minimal impact on the overall network measures.

[TABLE 2]

[FIGURES 2, 3]

In contrast, there were no structural covariance connections that were significantly different between Remitted and Non-Remitted patients at Week-4 and Week-22 (Week 4: p=0.40, Week 22: p=0.19; minimum FDR-corrected p-values). Furthermore, the NBS analysis did not identify any connected clusters of suprathreshold edges that differed between Remitted and Non-Remitted patients at either time-points (Week-4: extent=3, p=0.59; Week-22, extent=2, p=0.76). Consistent with this, global and local efficiency network measures were also unaffected by remission status at Week-4 (Table 3). Likewise eigenvector centrality measures were non-significant (Week-4: p=0.984, Week-22: p=0.981; minimum FDR-corrected p-values).

However, as discussed above, when directly investigating the network discovered using the Week-74 outcome, the LGI covariance was found to be reduced at these time points, as shown in Figure 2D, which depicts the fisher-z test effect size (Remission>non-Remission) for each of the network edges that differed between Remitted and Non-Remitted patients at Week-74.

Prediction Modelling

Support vector machine prediction models were not able to predict remission at better than chance rates at either Week-74 (balanced accuracy, sensitivity, specificity: 0.50, 0.23, 0.76), Week-22 (0.54, 0.45, 0.63) or Week-4 (0.51, 0.25, 0.78). The same was true for differentiating all patients from controls (0.48, 0.83, 0.12). A reference prediction of female gender (over both patient and control groups) demonstrated good cross-validated performance (balanced accuracy, sensitivity, specificity: 0.72, 0.59, 0.85) (see eFigure 1).

Removing low reliability features and restricting the model to patients with a minimal interval between undergoing MRI scanning and starting medication had no effect on prediction performance (see Supplementary Material).

Discussion

We used MRI at first presentation to evaluate the brain correlates of remission over the initial 17 months of treatment for psychosis. Our main finding was that likelihood of remission was related to alterations in gyrification-based connectivity networks only.

In the OPTiMiSE trial from which our sample was drawn, some patients who were classified as not in remission at Week-4 went on to achieve remission later on[1]. Of the subsample of patients who had MRI, about a quarter of those not in remission at Week-4 had subsequently moved into the remission category. Conversely, about a third of those in remission at Week-4 no longer met remission criteria at later timepoints. This instability of response status was more marked in the early than in the later stages after illness onset, and may explain why the MRI correlates of remission were most significant at the final assessment point.

It is interesting that we found no baseline localised differences in volumes, cortical thickness, surface area or local gyrification associated with lack of remission. An absence of localised differences in the presence of concomitant network alterations is consistent with previous evidence that therapeutic response at 24 weeks in first episode psychosis was not associated with measures of cortical thickness or subcortical volumes, but with altered structural network connectivity[8]. Alterations in cortical gyrification may reflect a neurodevelopmental disruption, as gyrification normally occurs in utero. Changes in gyrification networks may be related to a disorder of neural connectivity during brain maturation, for example at the stage of synaptic pruning and dendritic arborization[13-14, 15]. In the present study, the association between altered gyrification networks and a failure to achieve remission suggests that perturbed neurodevelopment could contribute to relatively poor clinical outcomes in a subgroup of patients.

We used structural covariance to evaluate gyrification-based brain network organisation, an approach that identifies positively correlated regional gyrification measures between pairs of brain regions, which is thought to index the inter-regional synchronization of developmental changes[16-18]. In patients who were not in remission at Week-74, there were reductions in structural connectivity over a distributed network of connections, particularly involving frontal and temporal regions. These effects were not strongly topological, and there were no significant differences in global or local efficiency measures between patients in remission and those not in remission.

To date, most studies of structural networks in psychosis have used measures of grey matter volumes (reviewed in[19]), although more recent studies have also examined cortical thickness[20-21]. In general, previous studies have reported increased network segregation and decreased integration (reduced efficiency) in patients with schizophrenia compared to controls. To our knowledge, the only studies to have investigated the relationship between cortical network properties and response to treatment were our previous study in first episode psychosis patients[7], and a study by Homan and colleagues[22] in patients treated for two years. Both found that symptomatic improvement was related to reduced nodal centrality of the left insula and the anterior cingulate. These regions were also involved in the network alterations we observed in patients not in remission, but mostly at the level of the edges, with the nodal centrality effect being only marginally significant. The NBS approach that we used may have improved our power to detect between group differences at the edge level[12].

In parallel to studies of structural connectivity, several investigations have examined the relationship between antipsychotic response and functional dysconnectivity, using resting state fMRI data. These studies suggest that the response to antipsychotic medication is related to functional dysconnectivity in pathways involving the anterior cingulate cortex, hippocampus, striatum and midbrain[23-27]. Our findings complement these data in that they suggest that response may also be linked to structural dysconnectivity. Moreover, the

regions involved in the respective networks appear to overlap, with connections to the anterior cingulate and frontal cortex altered in both[27, 28].

Overall, our data suggest that a poor treatment response in schizophrenia is related to altered connectivity across a distributed set of brain regions, rather than focal morphological alterations in a specific area. This is coherent with both the inconsistency and the large variability of findings reported in previous studies of focal neuromorphological correlates of psychosis outcomes[2]. Still, poor treatment response in first episode patients has previously been linked to reduced frontal gyrification[29-31], whereas we found no evidence of any regional differences at baseline between patients who later did and did not achieve remission. These negative findings are important, as our study was well-powered to detect a typical medium effect size if there was one (see eFigures 2 and 3). Indeed, they are consistent with some papers that have found no association between brain morphology and response to treatment, including in the early illness phases (see[32, 33] for review and meta-analysis). Variance across studies may be due to the use of non-standardised outcomes such as number of hospitalisation, symptom severity and reduction, or level of functioning; small sample sizes; variation in treatment approaches; and differences in neuroimaging and analytic approaches. Differences in findings may also reflect differences in the respective patient samples. For example, our previous reports of reduced localised gyrification in non responders derived from predominantly male patients with any type of psychosis and any duration of illness[31, 34], whereas the present study involved more female than male patients, was restricted to patients with a schizophrenia spectrum psychosis, and with an illness duration of less than 2 years. It is possible that alterations in gyrification in schizophrenia may be more evident in male than female patients, and in patients with a longer illness duration[34].

Our machine learning analyses indicated that brain structure at baseline did not predict remission at any of the stages we examined, similarly to another machine learning study

where remission after six weeks of amisulpride monotherapy could not be predicted[35]. This is however in contrast with another machine learning study from our group, where brain structure in first episode patients predicted symptom remission over the first 6 years of illness[36]. Of note, in that study patients were treated naturalistically with a variety of different antipsychotic medications at different doses, and there were fewer follow up assessments. In the present study, treatment was standardised, with a limited set of medications prescribed at set doses, and the assessments were relatively frequent, pointing to the importance of conducting these over long follow up periods.

Our study has several strengths. We examined a large sample of first episode patients who were either medication-naïve or had been minimally treated. All had a schizophrenia-spectrum psychosis, were scanned using the same MRI methodology, were treated using standardised protocols, and remission was assessed at multiple time points over the first 17 months of illness using well-established criteria.

Still, some limitations should also be considered. As this was a multicentre trial, the scans were acquired on different scanners, and site effects cannot be completely excluded. We sought to minimise these by using the ADNI protocol, which is specifically designed for multisite MRI studies, by regularly scanning phantoms at all centres, and by including site as a covariate in the statistical analyses (data available on request; see eFigure 3 for effect sizes). Also, the time span in the evaluation of remission is broad, and drop-outs may have had an effect on our analyses. Still, an additional analysis of only those subjects with a PANSS at week-74 (excluding drop-outs) showed the same direction of effect for all 29 edges identified as related to week 74 remission status in the structural covariance network. Also, we cannot exclude the possibility that the clinical teams changed the treatment in these drop-outs. Finally, our work focused only on brain structure, and did not investigate other neuroimaging markers that have been linked to treatment response, including alterations in

functional connectivity[23-25,27], striatal dopamine dysfunction[37-38], elevated anterior cingulate glutamate levels[39, 40].

In conclusion, these data suggest that the symptomatic remission in schizophrenia may be more related to alterations in brain connectivity than to focal morphometric changes. The prediction of treatment response may be facilitated by integrating MRI measures with other neuroimaging and peripheral blood measures that are candidate biomarkers for the therapeutic response[41].

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REFERENCES

1. Kahn RS, Winter van Rossum I, Leucht S, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* Oct 2018;5(10):797-807.

2. Dazzan P, Arango C, Fleischacker W, et al. Magnetic resonance imaging and the prediction of outcome in first-episode schizophrenia: a review of current evidence and directions for future research. *Schizophr Bull* May 2015;41(3):574-583.

3. Barry EF, Vanes LD, Andrews DS, Patel K, Horne CM, Mouchlianitis E, Hellyer PJ, Shergill SS. Mapping cortical surface features in treatment resistant schizophrenia with in vivo structural MRI. *Psychiatry Res* Apr 2019;274:335-344.

4. Jessen K, Rostrup E, Mandl RCW, Nielsen MO, Bak N, Fagerlund B, Glenthoj BY, Ebdrup BH. Cortical structures and their clinical correlates in antipsychotic-naive schizophrenia patients before and after 6 weeks of dopamine D2/3 receptor antagonist treatment. *Psychol Med* Apr 2019;49(5):754-763.

5. Palaniyappan L, Park B, Balain V, Dangi R, Liddle P. Abnormalities in structural covariance of cortical gyrification in schizophrenia. *Brain Struct Funct* Jul 2015;220(4):2059-2071.

6. Crossley NA, Marques TR, Taylor H, et al. Connectomic correlates of response to treatment in first-episode psychosis. *Brain* Feb 2017;140(2):487-496.

7. Palaniyappan L, Marques TR, Taylor H, et al. Globally Efficient Brain Organization and Treatment Response in Psychosis: A Connectomic Study of Gyrification. *Schizophr Bull* Nov 2016;42(6):1446-1456.

8. Doucet GE, Moser DA, Luber MJ, Leibu E, Frangou S. Baseline brain structural and functional predictors of clinical outcome in the early course of schizophrenia. *Mol Psychiatry* Oct 3 2018.

9. Andreasen NC, Carpenter WT, Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* Mar 2005;162(3):441-449.

10. Schaer M, Cuadra MB, Schmansky N, Fischl B, Thiran JP, Eliez S. How to measure cortical folding from MR images: a step-by-step tutorial to compute local gyrification index. *J Vis Exp* Jan 2 2012(59):e3417.

11. Klein A, Tourville J. 101 labeled brain images and a consistent human cortical labeling protocol. *Front Neurosci* 2012;6:171.

12. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage* Dec 2010;53(4):1197-1207.

13. White T, Hilgetag CC. Gyrification and neural connectivity in schizophrenia. *Dev Psychopathol* Feb 2011;23(1):339-352.

14. Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, Schlaggar BL, Petersen SE. Functional brain networks develop from a "local to distributed" organization. *PLoS Comput Biol* May 2009;5(5):e1000381.

15. Power JD, Fair DA, Schlaggar BL, Petersen SE. The development of human functional brain networks. *Neuron* Sep 9 2010;67(5):735-748.

16. Alexander-Bloch A, Raznahan A, Bullmore E, Giedd J. The convergence of maturational change and structural covariance in human cortical networks. *J Neurosci* Feb 13 2013;33(7):2889-2899.

17. Khundrakpam BS, Reid A, Brauer J, et al. Developmental changes in organization of structural brain networks. *Cereb Cortex* Sep 2013;23(9):2072-2085.

18. Zielinski BA, Gennatas ED, Zhou J, Seeley WW. Network-level structural covariance in the developing brain. *Proc Natl Acad Sci U S A* Oct 19 2010;107(42):18191-18196.

19. Wheeler AL, Voineskos AN. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. *Front Hum Neurosci* 2014;8:653.

20. Wannan CMJ, Cropley VL, Chakravarty MM, et al. Evidence for Network-Based Cortical Thickness Reductions in Schizophrenia. *Am J Psychiatry* Jul 1 2019;176(7):552-563.

21. Makowski C, Lewis JD, Lepage C, Malla AK, Joober R, Lepage M, Evans AC. Structural Associations of Cortical Contrast and Thickness in First Episode Psychosis. *Cereb Cortex* Mar 7 2019.

22. Homan P, Argyelan M, DeRosse P, et al. Structural similarity networks predict clinical outcome in early-phase psychosis. *Neuropsychopharmacology* Apr 2019;44(5):915-922.

23. Anticevic A, Hu X, Xiao Y, et al. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. *J Neurosci* Jan 7 2015;35(1):267-286.

24. Hadley JA, Nenert R, Kraguljac NV, Bolding MS, White DM, Skidmore FM, Visscher KM, Lahti AC. Ventral tegmental area/midbrain functional connectivity and response to antipsychotic medication in schizophrenia. *Neuropsychopharmacology* Mar 2014;39(4):1020-1030.

25. Kraguljac NV, White DM, Hadley JA, Visscher K, Knight D, ver Hoef L, Falola B, Lahti AC. Abnormalities in large scale functional networks in unmedicated patients with schizophrenia and effects of risperidone. *Neuroimage Clin* 2016;10:146-158.

26. Lottman KK, Kraguljac NV, White DM, Morgan CJ, Calhoun VD, Butt A, Lahti AC. Risperidone Effects on Brain Dynamic Connectivity-A Prospective Resting-State fMRI Study in Schizophrenia. *Front Psychiatry* 2017;8:14.

27. Sarpal DK, Argyelan M, Robinson DG, et al. Baseline Striatal Functional Connectivity as a Predictor of Response to Antipsychotic Drug Treatment. *Am J Psychiatry* Jan 2016;173(1):69-77.

28. Cadena EJ, White DM, Kraguljac NV, Reid MA, Jindal R, Pixley RM, Lahti AC. Cognitive control network dysconnectivity and response to antipsychotic treatment in schizophrenia. *Schizophr Res* Feb 2019;204:262-270.

29. Cao B, Mwangi B, Passos IC, et al. Lifespan Gyrification Trajectories of Human Brain in Healthy Individuals and Patients with Major Psychiatric Disorders. *Sci Rep* Mar 30 2017;7(1):511.

30. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. *Biol Psychiatry* May 15 2011;69(10):974-979.

31. Palaniyappan L, Marques TR, Taylor H, et al. Cortical folding defects as markers of poor treatment response in first-episode psychosis. *JAMA Psychiatry* Oct 2013;70(10):1031-1040.

32. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* Sep 2013;37(8):1680-1691.

33. Tarcijonas G, Sarpal DK. Neuroimaging markers of antipsychotic treatment response in schizophrenia: An overview of magnetic resonance imaging studies. *Neurobiol Dis* Nov 2019;131:104209.

34. Yucel M, Stuart GW, Maruff P, Velakoulis D, Crowe SF, Savage G, Pantelis C. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: an MRI morphometric study. *Cereb Cortex* Jan 2001;11(1):17-25.

35. Ebdrup BH, Axelsen MC, Bak N, et al. Accuracy of diagnostic classification algorithms using cognitive-, electrophysiological-, and neuroanatomical data in antipsychotic-naive schizophrenia patients. *Psychol Med* Dec 2019;49(16):2754-2763.

36. Mourao-Miranda J, Reinders AA, Rocha-Rego V, et al. Individualized prediction of illness course at the first psychotic episode: a support vector machine MRI study. *Psychol Med* May 2012;42(5):1037-1047.

37. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* Nov 2012;169(11):1203-1210.

38. Jauhar S, McCutcheon R, Borgan F, et al. The relationship between cortical glutamate and striatal dopamine in first-episode psychosis: a cross-sectional multimodal PET and magnetic resonance spectroscopy imaging study. *Lancet Psychiatry* Oct 2018;5(10):816-823.

39. Egerton A, Brugger S, Raffin M, Barker GJ, Lythgoe DJ, McGuire PK, Stone JM. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. *Neuropsychopharmacology* Oct 2012;37(11):2515-2521.

40. Egerton A, Broberg BV, Van Haren N, et al. Response to initial antipsychotic treatment in first episode psychosis is related to anterior cingulate glutamate levels: a multicentre (1)H-MRS study (OPTiMiSE). *Mol Psychiatry* Nov 2018;23(11):2145-2155.

41. McGuire P, Dazzan P. Does neuroimaging have a role in predicting outcomes in psychosis? *World Psychiatry* Jun 2017;16(2):209-210.

Figure legends

Figure 1: Sankey diagram of Remission Status

Remission status flow diagram for the 3 study remission observations. Box and flow widths are proportionate to the number of patients given in brackets as [n]. Flows are coloured by the remission status at the target (blue = Non-Remitted, yellow = Remitted). Remission status is determined from PANSS scores using modified Andreasen criteria. Week-22 and Week-74 flows include last available PANSS observation data (at Week-22 this was used for 42 patients, with 29 Remitted at last observation; at Week-74 this was used for 62 patients, with 33 remitted at last observation).

Figure 2: LGI Network Correlations and Week-74 Remission

To illustrate the origin of network edge differences, bivariate scatterplots of local gyrification indices underlying 2 of the significantly affected edges in the LGI structural covariance network are displayed. Values on the x and y axes are residualised for covariates and then for display standardised to the mean and standard deviation of the control group. Ellipses show the 95% confidence ellipse centred on the mean. Lines are OLS regression fits.

Figure 3: Disturbed LGI Network Edges and Week-74 Remission

A shows an axial view of the LGI covariance network. Nodes are arranged according to the region's centre of gravity with minor adjustments to reduce overlap. A key to region labels is provided in eTable5. Edges most affected by participants Week-74 Remission status are shown in red. Solid red lines (n=29) indicate significant edges (NBS $p<0.05$, network forming threshold $p<0.005$). For reference, grey edges display the control group network thresholded at 15% density (the lowest connected density threshold). The background image is a rendering of the pial surfaces. **B** shows an alternate view of the network presented in A: a rotated sagittal view of the left frontal regions where most significant differences were seen.

C shows the evolution of the remission-related differences in the edges of the affected network at Week-74. Although a statistically significant effect did not emerge at Week-4 or Week-22, LGI covariance was reduced. **D** a spaghetti plot showing a consistent evolution of the fisher-z test effect size (Remission > nonRemission), for each of the network edges which were observed to differ between remission and non-remission at Week-74. Of note, some edges are as impacted as Z=3 ($p<0.005$ uncorrected) at Week-4.

Table 1: Socio-demographic and clinical details of patients at each time-point

		Week-4			Week-22			Week-74		
	All Patients (n=154)	**Non-Remitted (n=46)**	**Remitted (n=108)**	**Test Result**	**Non-Remitted (n=69)**	**Remitted (n=85)**	**Test Result**	**Non-Remitted (n=57)**	**Remitted (n=97)**	**Test Result**
Age (Years)	25.3 (6.10)	23.2 (5.4)	26.2 (6.14)	0.003	24.3 (5.9)	26.1 (6.16)	0.056	24.5 (6.42)	25.8 (5.88)	0.220
Female Sex	53 (34.4%)	17 (37%)	36 (33.3%)	0.804	22 (32%)	31 (37%)	0.671	16 (28%)	37 (38%)	0.274
Education (Years)	12 [10;13]	12 [10;14]	12 [10;13]	0.768	12.0 [10.0;13.0]	12.0 [10.0;13.8]	0.257	11.5 [10;13]	12 [10;14]	0.122
eTIV (ml)	1501 (167)	1499 (166)	1501 (168)	0.935	1501 (177)	1500 (159)	0.985	1516 (170)	1492 (165)	0.401
Scan Timing (Days)	1 [0;7]	0 [0;5.75]	1 [0;7]	0.390	1 [0;5]	1 [0;7]	0.980	1 [0;7]	1 [0;6]	0.865
AP Naïve	64 (41.6%)	20 (44%)	44 (40.7%)	0.891	32 (46%)	32 (38%)	0.353	26 (46%)	38 (39.)	0.540
Illness Duration (Months)	4 [2;7]	4 [2;11.5]	3 [2;6.25]	0.594	4 [2;10]	3 [2;6]	0.080	4 [2;10.5]	3 [2;6]	0.266
Baseline PANSS:										
Total	70.3 (16.6)	79.2 (14.6)	66.5 (16.0)	<0.001	74.8 (16.4)	66.7 (16.1)	0.002	74.9 (16.1)	67.6 (16.4)	0.008
Positive	18.7 (5.33)	21.4 (4.66)	17.5 (5.19)	<0.001	19.8 (5.14)	17.7 (5.33)	0.016	19.2 (4.80)	18.3 (5.61)	0.300
Negative	16.6 (6.61)	19.7 (6.43)	15.2 (6.25)	<0.001	18.4 (6.61)	15.1 (6.27)	0.002	18.9 (6.97)	15.2 (6.03)	0.001
General	35.0 (8.59)	38.1 (8.02)	33.7 (8.52)	0.003	36.5 (8.21)	33.8 (8.74)	0.049	36.8 (8.40)	34.0 (8.57)	0.051
Weeks to Evaluation of Remission	-	4.07 [3.9;4.7]	4.3 [4.0;5.0]	0.173	17.0[11.0;20.6]	16.6[5.1;18.0]	0.071	27.4 [10.3;73.7]	66.1 [9.1;74.7]	0.225

For approximately normal data, mean (SD) is presented with t-tests. For categorical data, frequency (percentage %) is presented with Fisher's exact tests. For duration data, median [25th percentile; 75th percentile] is presented with Kruskall-Wallis test. eTIV = Freesurfer estimated total intracranial volume. AP Naïve = Antipsychotic medication naïve at point of study recruitment. Scan Timing (days) = number of days on study medication before MRI. Weeks to evaluation of remission = time in weeks (relative to study baseline) at which remission status was determined. Illness Duration (Months) = duration in months of current psychotic episode, less any periods of antipsychotic treatment.

Table 2: Week-74 Remission status and NBS Network Edges

		Pearson's r			Non-Remitted – Remitted Effect		
Label Region 1	**Label Region 2**	**Non-Remitted**	**Remitted**	**Controls**	**Difference**	**Fisher-Z**	**Permutation p-value**
lh_INS	lh_rACC	-0.034	0.577	0.335	-0.61	-4.06	0.0001
lh_rACC	lh_IFGorb	-0.219	0.422	0.332	-0.64	-3.94	0.0001
lh_SFG	lh_cACC	0.396	0.784	0.627	-0.39	-3.72	0.0001
lh_rACC	lh_IFGoper	-0.034	0.515	0.246	-0.55	-3.53	0.0001
lh_preCEN	lh_PCC	0.064	0.573	0.373	-0.51	-3.44	0.0001
lh_mOFC	lh_MOG	-0.056	0.485	0.334	-0.54	-3.43	0.0004
lh_STG	lh_rACC	0.011	0.528	0.382	-0.52	-3.38	0.0002
lh_INS	lh_PCC	-0.031	0.486	0.312	-0.52	-3.29	0.0006
lh_IFGorb	lh_IPG	0.020	0.519	0.355	-0.50	-3.26	0.0001
lh_rACC	lh_preCEN	0.141	0.601	0.466	-0.46	-3.24	0.0002
lh_SFG	lh_PCC	0.201	0.634	0.428	-0.43	-3.18	0.0012
lh_SFG	lh_rACC	0.456	0.774	0.661	-0.32	-3.16	0.0001
lh_rACC	lh_MOG	0.043	0.522	0.452	-0.48	-3.14	0.0009
lh_TTG	lh_rACC	0.016	0.501	0.322	-0.49	-3.13	0.0002
lh_paraCEN	lh_mOFC	0.074	0.541	0.397	-0.47	-3.11	0.0009
rh_ITG	lh_mOFC	-0.124	0.385	0.299	-0.51	-3.11	0.0003
lh_IFGorb	lh_cACC	-0.110	0.397	0.315	-0.51	-3.11	0.0026
lh_rACC	lh_IFGtri	-0.026	0.462	0.238	-0.49	-3.08	0.0009
lh_INS	lh_cACC	0.052	0.512	0.319	-0.46	-3.01	0.0033
lh_paraHC	lh_mOFC	-0.190	0.309	0.208	-0.50	-2.99	0.0026
rh_IPG	lh_IFGorb	0.044	0.502	0.418	-0.46	-2.98	0.0006
lh_rACC	lh_postCEN	0.053	0.506	0.410	-0.45	-2.95	0.0009
lh_STG	lh_mOFC	0.093	0.535	0.390	-0.44	-2.95	0.0005
rh_IPG	lh_mOFC	-0.008	0.457	0.401	-0.46	-2.94	0.0022
rh_SMG	lh_IFGorb	0.083	0.518	0.466	-0.43	-2.87	0.0042
lh_SMG	lh_rACC	0.015	0.465	0.347	-0.45	-2.87	0.0012
lh_PCC	lh_IFGtri	-0.107	0.363	0.191	-0.47	-2.85	0.0047
rh_postCEN	lh_IFGorb	0.051	0.491	0.535	-0.44	-2.85	0.0013
lh_IFGorb	lh_mOFC	-0.056	0.401	0.351	-0.46	-2.82	0.0010

Region 1/2 ordering is arbitrary as correlation is symmetrical. Table is sorted by Fisher Z effect size. Permutation p-values from k=10,000 permutations of group label (uncorrected for multiple comparisons). For a key to region labels see eTable S5.

Table 3: Global and local efficiency measures at each time point.

	Remitted	Non-remitted	P value
Week-4			
Global efficiency AUC	0.155	0.136	p=0.09
Local efficiency AUC	0.214	0.193	p=0.16
Week-22			
Global efficiency AUC	0.155	0.145	p=0.28
Local efficiency AUC	0.217	0.195	p=0.09
Week-74			
Global efficiency AUC	0.154	0.140	p=0.17
Local efficiency AUC	0.214	0.193	p=0.12

Conflict of Interest

C. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Sanofi, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda.

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S. Galderisi has been a consultant and/or advisor to or has received honoraria or grants from: Millennium Pharmaceuticals, Innova Pharma-Recordati Group, Janssen Pharmaceutica NV, Sunovion Pharmarmaceuticals, Janssen-Cilag Polska Sp. zo. o., Gedeon Richter-Recordati, Pierre Fabre, Otsuka, Angelini.

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C. Pantelis served on an advisory board for Lundbeck, Australia Pty Ltd. He has received honoraria for talks presented at educational meetings organized by Lundbeck. He was supported by a NHMRC Senior Principal Research Fellowship (ID: 1105825), a NHMRC Program Grant (ID: 1150083), and by a grant from the Lundbeck Foundation (ID: R246-2016-3237).

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