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# Connectome organization is related to longitudinal changes in general functioning, symptoms and IQ in chronic schizophrenia

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ABSTRACT

Emerging evidence suggests schizophrenia to involve widespread alterations in the macroscale wiring architecture of the human connectome. Recent findings of attenuated connectome alterations in unaffected siblings of schizophrenia patients suggest that altered connectome organization may relate to the vulnerability to develop the disorder, but whether it relates to progression of illness after disease onset is currently unknown. Here, we examined the interaction between connectome structure and longitudinal changes in general functioning, clinical symptoms and IQ in the 3 years following MRI assessment in a group of chronically ill schizophrenia patients. Effects in patients were compared to associations between connectome organization and changes in subclinical symptoms and IQ in healthy controls and unaffected siblings of schizophrenia patients. Analyzing the patient sample revealed a relationship between structural connectivity—particularly among central 'brain hubs'—and progressive changes in general functioning ($p = 0.007$), suggesting that more prominent impairments of hub connectivity may herald future functional decline. Our findings further indicate that affected local connectome organization relates to longitudinal increases in overall PANSS symptoms ($p = 0.013$) and decreases in total IQ ($p = 0.003$), independent of baseline symptoms and IQ. No significant associations were observed in controls and siblings, suggesting that the findings in patients represent effects of ongoing illness, as opposed to normal time-related changes. In all, our findings suggest connectome structure to have predictive value for the course of illness in schizophrenia.



## 1. Introduction

Schizophrenia's etiology has long since been related to alterations in the wiring architecture of the brain's network (Stephan et al., 2009; Rubinov and Bassett, 2011; Van den Heuvel and Kahn, 2011; Fornito et al., 2012; Van den Heuvel and Fornito, 2014; Wheeler and Voineskos, 2014). A comprehensive map of the white matter pathways connecting disparate areas of the human brain is referred to as the macroscale connectome (Hagmann, 2005; Sporns et al., 2005). Emerging evidence on connectome structure in schizophrenia suggests disease-related changes to include affected neural communication, aberrant local organization and modular structure and a less central position of brain hubs (Bassett et al., 2008; Lynall et al., 2010; Skudlarski et al., 2010; Van den Heuvel et al., 2010). These putative brain hubs have been suggested to reside in multimodal association areas of the cortex, to participate in complex and diverse neuronal communication (Rubinov and Bullmore, 2013; Van den Heuvel and Sporns, 2013; De Reus and Van den Heuvel, 2014; Senden et al., 2014) and to be mutually connected into a core collective referred to as a 'rich club' (Van den Heuvel and Sporns, 2011; Van den Heuvel et al., 2012). The white matter pathways comprising this central communication system have been suggested to be disproportionally affected in schizophrenia (Van den Heuvel et al., 2013). Moreover, unaffected siblings of patients to show similar, though attenuated, effects (Collin et al., 2014). Such findings of connectome alterations in first-degree relatives (Repovs et al., 2011; Fornito et al., 2013; Collin et al., 2014), who are at increased genetic risk for schizophrenia but lack the potential impact of (untreated) psychosis (Cahn et al., 2009) and psychotropic medication (Nejad et al., 2012; Vita et al., 2012), have led to the hypothesis that affected connectome organization might be reflective of an inherited neurodevelopmental vulnerability to the disorder (Collin and Van den Heuvel, 2013; Skudlarski et al., 2013; Van den Heuvel and Fornito, 2014).

Cross-sectional investigations of brain network organization in relation to illness severity in schizophrenia have suggested global and local network efficiency to be related to severity of both positive (Wang et al., 2012) and negative (Yu et al., 2011; Wang et al., 2012) symptoms. In

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addition, reduced levels of functional network cost-efficiency have been associated with poorer working memory performance (Bassett et al., 2009). An open question regarding connectome abnormalities in schizophrenia (Dauvermann et al., 2014)—altered hub connectivity in particular (Van den Heuvel and Kahn, 2011)—is whether, and if so how, alterations in macroscale connectome wiring relate to illness progression and outcome. Persistent symptoms (Lieberman, 1999) and real-world deficits in areas such as employment (Harvey and Velligan, 2011) and everyday living (Harvey et al., 2009; Leifker et al., 2009) are common in patients, but prognosis at the individual level is heterogeneous (Schultz and Andreasen, 1999). Relating connectome architecture to progression of illness and functional deficits might inform prognostic estimations. In this longitudinal study, a group of schizophrenia patients, investigated previously in two cross-sectional connectome studies (Van den Heuvel et al., 2013; Collin et al., 2014), was reassessed after 3 years follow-up. Changes over time in general and intellectual functioning and clinical symptoms were evaluated and related to connectome structure at baseline. Particular emphasis was placed on examining the predictive value of measures of connectome topology (e.g., clustering, global efficiency and rich club organization) in terms of illness progression in the 3 years following MRI assessment.

## 2. Materials and methods

### 2.1. Participants

A sample of 30 schizophrenia patients, from a total sample of 40 patients of whom diffusion-weighted imaging data were examined previously as part of two studies on connectome architecture in patients (Van den Heuvel et al., 2013) and their unaffected siblings (Collin et al., 2014), were included in the current study. Longitudinal data on functional outcome, IQ and symptomatology at 3-year follow-up were examined in relation to connectome structure. In addition, from the baseline sample containing 51 healthy controls and 54 unaffected siblings of patients (Collin et al., 2014), 45 controls and 48 siblings were reassessed after 3 years and included in the current study. In these subjects, longitudinal changes in IQ and subclinical psychotic symptoms were investigated for a link with connectome structure, to disentangle disease-related effects from 'normal' changes with time in unaffected subjects, in absence/presence of increased familial risk for schizophrenia. All participants were recruited at the University Medical Center Utrecht, as part of a longitudinal study on schizophrenia in the Netherlands (Genetic Risk and Outcome of Psychosis, or 'GROUP', study) (Korver et al., 2012). The affiliated medical ethics committee approved the study and all subjects provided written informed consent prior to participation.

### 2.2. Clinical measures

#### 2.2.1. Clinical measurements at time of scan acquisition and follow-up

All subjects were assessed at two time points: (1) at the time of MRI acquisition (T-MRI) and (2) at 3-year follow-up (T-FU). At both assessments, current and lifetime psychopathology was established using the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992). Patients met Diagnostic and Statistical Manual of Mental Disorders (DSM) fourth edition (American Psychiatric Association, 2000) criteria for schizophrenia or related spectrum disorders at T-MRI. Siblings had no diagnosis of a current or lifetime psychotic disorder, including bipolar disorder. Healthy controls had no current or lifetime psychotic disorder and no first- or second-degree family member with a lifetime psychotic disorder. The baseline characteristics of the total sample of patients, siblings and controls ($N = 145$) from our previous cross-sectional study were described in detail in (Collin et al., 2014). The baseline characteristics of those subjects that were reevaluated at T-FU ($N = 30$ patients, $N = 48$ siblings, $N = 45$ controls) are provided in the Supplementary material.

For all study participants, total IQ was estimated using four subtests of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS): Vocabulary, Comprehension, Block Design and Picture Arrangement (Stinissen et al., 1970). For patients, the type and chlorpromazine equivalent daily dose of antipsychotic medication was recorded, symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and symptom remission (Andreasen et al., 2005), employment and living arrangements were recorded as indices of overall functioning. In controls and siblings, the Community Assessment of Psychic Experiences (CAPE) was used to assess subclinical symptoms (Stefanis et al., 2002). All clinical characteristics were assessed at both time points, and differences between the T-MRI and T-FU were tested for statistical significance using paired samples t-tests for continuous and McNemar's chi-square tests for (bi-) nominal variables (McCrum-Gardner, 2008) (Table 1).

#### 2.2.2. Longitudinal changes in general functioning, symptoms and IQ

General functioning (GF) of patients was determined at T-MRI and T-FU by combining data on three intuitive measures of functioning: employment, independent living and symptom remission (Fig. 1a, see Supplementary material for details). GF was computed at both time points as a composite score between 0 (meeting none of the requirements) and 3 (employed, living independently and in symptomatic remission), and longitudinal change in GF was computed as the difference between assessments. Four major trajectories of change in GF during follow-up were discerned: increased GF at T-FU as compared to T-MRI ($N = 5$), stable GF ($N = 12$), minor decrease in GF ($N = 11$) and major decrease (i.e., dropping two levels between T-MRI and T-FU) in GF ($N = 2$) (Fig. 1b). Patients were grouped according to the trajectory

**Table 1**
Demographic and clinical characteristics at the time of MRI assessment (T-MRI) and 3-year follow-up (T-FU) of patients evaluated at both time points (N = 30).

| | Time of scan | 3-year follow-up | p |
|---|---|---|---|
| Age in years, mean (SD) [range] | 30.6 (6.3) [22–45] | 33.7 (6.3) [25–48] | <.01 |
| Gender, M/F | 27/3 | 27/3 | N/A |
| DSM-diagnosis | | | |
| Schizophrenia, *N* (%) | 24 (80.0%) | 24 (80.0%) | 1.0 |
| Schizoaffective disorder, *N* (%) | 5 (16.7%) | 3 (10.0%) | .5 |
| Other schizophrenia spectrum, *N* (%) | 1 (3.3%) | 2 (6.7%) | 1.0 |
| Bipolar disorder, *N* (%) | 0 (0%) | 1 (3.3%) | N/A |
| Duration of illness, mean (SD) [range] | 8.1 (4.2) [2.5–18.3] | 11.2 (4.2) [5.9–21.0] | <.01 |
| IQ, mean (SD) [range] | 99.5 (15.0) [71–132] | 96.7 (16.4) [63–128] | .09 |
| PANSS total symptoms | 46.2 (11.6) [30–83] | 56.3 (14.9) [31–80] | <.01 |
| Remission | | | |
| Symptomatic remission, yes/no | 19/11 | 12/18 | .07 |
| Formal remission[a], yes/no | 7/21[e] | 7/23 | 1.0 |
| Employment (paid), yes/no | 19/11 | 16/14 | .13 |
| Household, independent/dependent | 16/14 | 18/12 | .50 |
| Living single/with partner | 14/2 | 17/1 | 1.0 |
| Living with parents/sheltered/other[b] | 8/4/2 | 5/6/1 | .39 |
| Antipsychotic medication | | | |
| Clozapine/other atypical[c]/typical/none | 7/20/1/1[f, g] | 7/20/1/0[e] | .56 |
| CPZ[d] equivalent dose, mean (SD) [range] | 256.7 (141.4) [50–625][g] | 266.3 (213.4) [50–1067] | .80 |

[a] Formal remission is defined as symptomatic remission during at least 6 months.
[b] Other household includes hospitalization, homelessness, living with sister.
[c] Other atypical medication includes risperidone, olanzapine, quetiapine and aripiprazole.
[d] CPZ = chlorpromazine.
[e] Data missing for $N = 2$.
[f] Data missing for $N = 1$.
[g] Data complemented at follow-up for two subjects.



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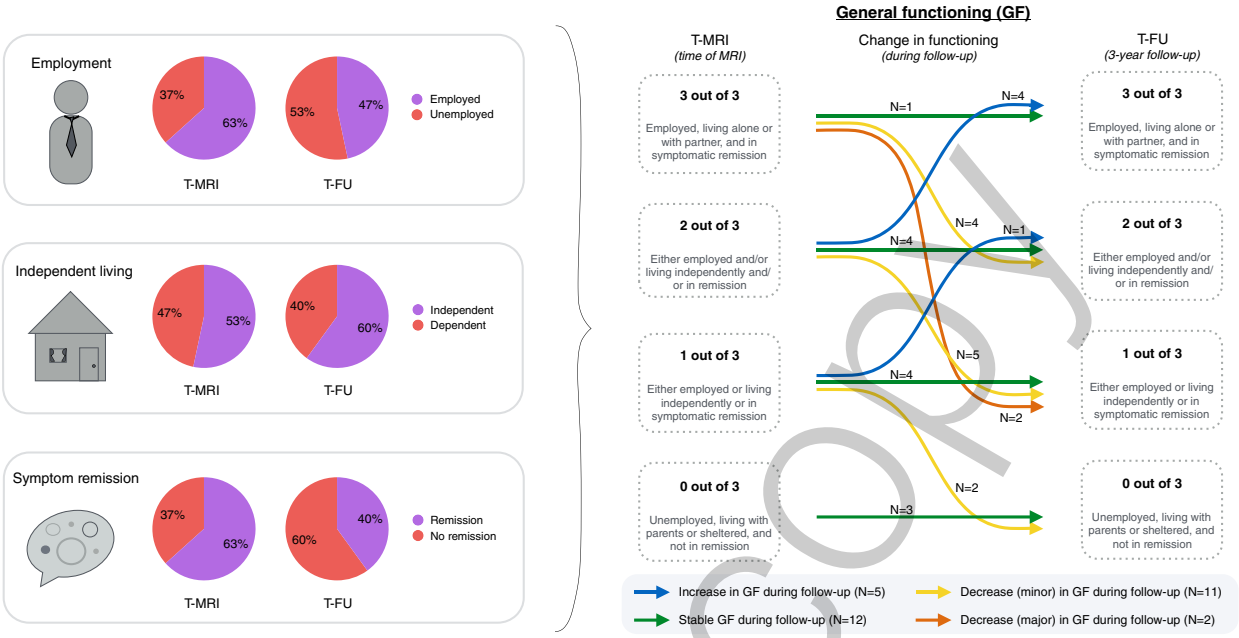


**Fig. 1.** Three intuitive measures of real-world functioning in schizophrenia (employment, independent living and symptom remission) were combined in one composite measure of general functioning (GF). GF was assessed at the time of MRI acquisition (T-MRI) and 3-year follow-up (T-FU). Four major trajectories of change in GF during follow-up were discerned (increase in GF, stable GF, minor decrease in GF, major decrease in GF) and patients were grouped accordingly.

of change in GF during follow-up. Differences between groups in demographic and clinical characteristics were tested for statistical significance using Kruskal–Wallis ANOVA for continuous and chi-square tests for categorical variables.

In addition, longitudinal changes in IQ and symptoms, computed as the difference in total IQ and total PANSS symptoms between T-MRI and T-FU, were examined. IQ changes in patients were compared to 'normal' differences between IQ measurements in unaffected subjects. Longitudinal changes in subclinical symptoms, as assessed by the difference in total CAPE symptoms between T-MRI and T-FU, were investigated in controls and siblings.

### 2.3. Neuroimaging

Neuroimaging involved acquisition of 1.5-T magnetic resonance imaging (MRI) scans, including an anatomical T1 scan (TE/TR 4.6/30 ms, flip angle 30°, 160–180 contiguous slices, 1 × 1 × 1.2 mm voxels, FOV = 256 mm, SENSE 1.5/1.5) and a diffusion-weighted imaging (DWI) scan with each two sets of 8 unweighted scans ($b$-factor = 0 s/mm2, TE/TR 88/9822 ms, parallel imaging factor: 2.5; flip angle 90, 60 slices, 2.5 mm isotropic voxels, no slice gap, FOV 240 mm, 128 × 128 reconstruction matrix) and 32 diffusion-weighted images (non-collinear, $b$-factor = 1000 s/mm$^2$) (Van den Heuvel et al., 2010; Mandl et al., 2013). Preprocessing of the T1 and DWI data (described in detail in the Supplementary material) included parcellation of the cerebral cortex into 68 cortical regions (i.e., 34 per hemisphere) using Freesurfer software (Fischl, 2012) and deterministic fiber tracking (Mori and Van Zijl, 2002) to reconstruct white matter pathways. Fiber tracking, in short, involved starting seeds in each voxel, subsequently following the preferred diffusion direction from one voxel to the next, to generate a total collection of streamlines reflective of the underlying white matter anatomy (Van den Heuvel et al., 2013; Collin et al., 2014).

### 2.4. Connectome evaluation

#### 2.4.1. Connectome reconstruction

Connectome reconstructions were taken from (Van den Heuvel et al., 2013; Collin et al., 2014). In short, for each individual dataset, a connectome map was reconstructed from the collection of parcellated cortical regions and reconstructed white matter streamlines, resulting in a matrix describing the level of structural connectivity between each pair of brain regions (Fig. 2a). Each connectome map was represented as a graph G = (V, E) consisting of a set of nodes V (representing 68 cortical regions) and connections E between nodes (reflecting cortico-cortical connections between regions) weighted according to the number of reconstructed streamlines (NOS) (Fig. 2b). Connections consisting of 5 or more streamlines were included as cortico-cortical pathways, effectively reducing the inclusion of potentially false positive registrations (De Reus and van den Heuvel, 2013a).

#### 2.4.2. Connectome examination

Connectome reconstructions were examined in terms of a number of graph attributes, together providing a description of the networks' overall architecture (Fig. 2c). Common descriptive graph metrics were investigated in relation to longitudinal changes in GF, symptoms and IQ: Overall connectivity $S$, describing the total level of connectivity strength of the reconstructed network; clustering $C$, providing an estimate of local information segregation, computed as the average likelihood that two neighbors of a node are mutually connected; global efficiency GE, an estimate of overall communication efficiency throughout the network, computed as the average inverse shortest path between each possible pair of nodes in the graph. Graph metrics were computed from NOS weighted networks (Rubinov and Sporns, 2010). Previous cross-sectional analysis of the metrics describing global connectome architecture in these subjects indicated significant reductions in $S$, GE and $C$ in patients, and intermediate levels of connectome clustering in unaffected siblings of patients (see Collin et al., 2014).

#### 2.4.3. Rich club organization

Rich club organization implies that hubs (i.e., highly connected and central nodes) are more densely mutually interconnected than is to be expected based on their high degree alone (Colizza et al., 2006; van den Heuvel and Sporns, 2011). Studies have shown the neural networks of several species to possess such an organization (Zamora-López et al., 2009; Harriger et al., 2012; De Reus and Van den Heuvel, 2013b; Shanahan et al., 2013; Towlson et al., 2013; Scholtens et al., 2014; Van

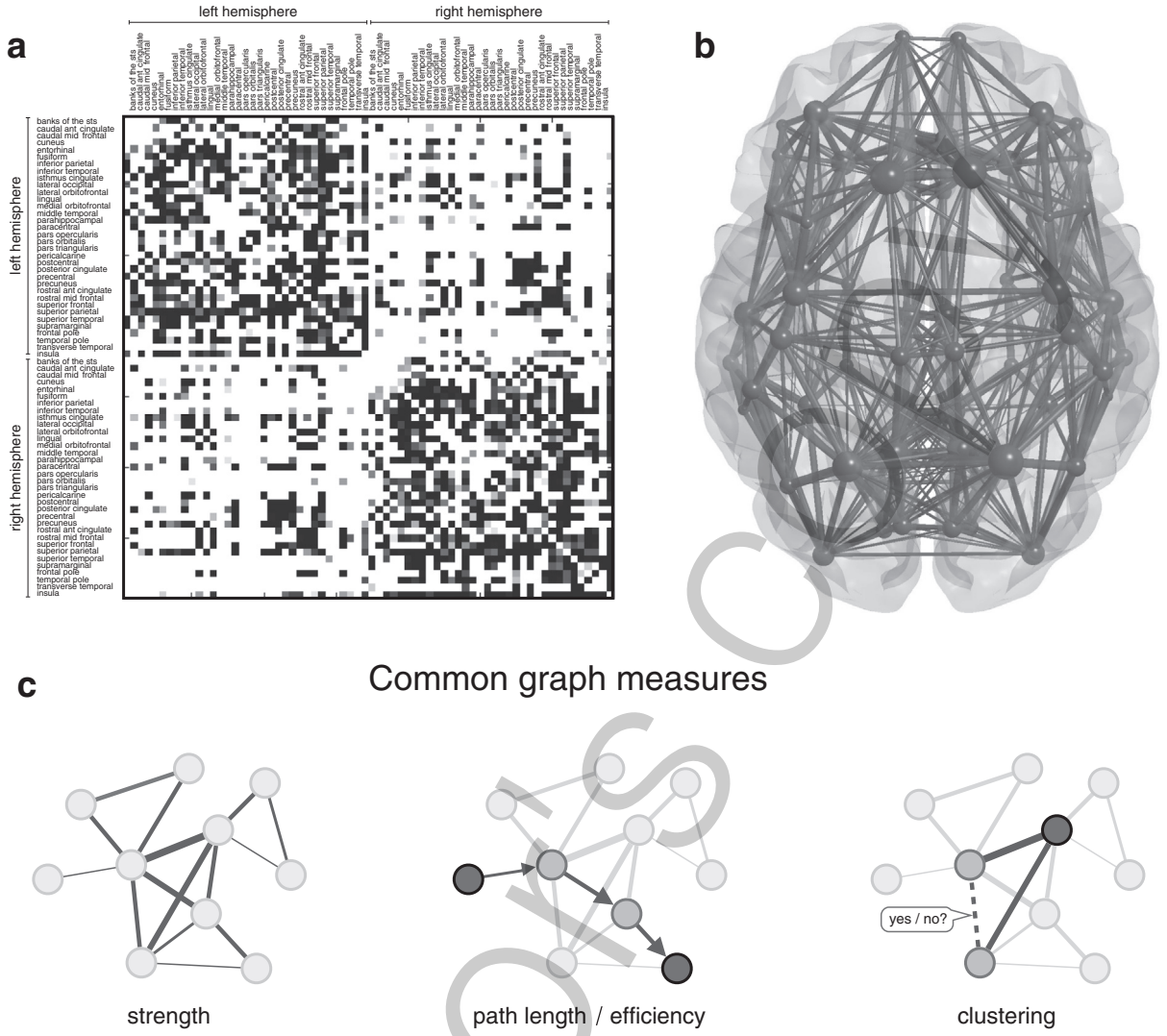


**Fig. 2.** Connectome map, depicted as a matrix (a) and neural graph (b), with rows/columns (a) and nodes (b) representing parcellated cortical brain regions ($N = 68$), and edges (b) and matrix entries (a) representing cortico-cortical connections, were examined using common graph metrics (c): strength, reflecting the total level of connectivity; global efficiency, describing overall communication efficiency in the network, computed as the average inverse shortest path length; clustering, providing an estimate of local information segregation.

den Heuvel and De Reus, 2014), and the level of connectivity within this system is reduced in schizophrenia patients (Van den Heuvel et al., 2013) and their siblings (Collin et al., 2014). In this study, hubs were a priori defined as the superior frontal and parietal gyrus, precuneus and insula bilaterally (as taken from Collin et al., 2014; Van den Heuvel et al., 2013), regions well validated as key brain hubs in previous research (Van den Heuvel and Sporns, 2013) (see Supplementary material for details). Based on the classification of networks nodes into 'hubs' and 'non-hubs', network edges were sub-divided into connection classes based on their participation in rich club formation, as 'rich club' connections (connecting hubs), 'feeder' connections (linking hubs to non-hubs) and 'local' connections (connecting non-hubs) (Van den Heuvel et al., 2012). The computation of rich club organization was taken from (Collin et al., 2014) and examined here in relation to longitudinal changes in clinical measures.

### 2.5. Statistical analysis

Measures of connectome organization were examined in terms of their relationship with longitudinal changes in GF, clinical symptoms and IQ. Specifically, it was examined whether the most intact connectome at T-MRI belonged to subjects who show increased GF at T-FU, the most affected networks to those showing progressive decrease in GF over time, with intermediate network metrics in subjects showing stable GF. Non-parametric Jonckheere Terpstra permutation analysis (Bewick et al., 2004)- for details, see (Collin et al., 2014)- was performed to test ordered differences in connectome impairments across groups signifying the extent of longitudinal change in GF. In addition, Pearson's correlations were computed to examine linear associations between connectome organization and subsequent changes in IQ and (sub)clinical symptoms. As connectome measures are related to overall connectivity, partial correlations with $C$ and GE, with overall connectivity included as a covariate, were also computed. Results were subjected to a false discovery rate (FDR) threshold of $q < 0.05$, indicating statistical significance. Findings with a $p < 0.05$ not reaching the FDR-threshold were interpreted as trend-level findings.

## 3. Results

### 3.1. Clinical measurements at time of scan acquisition and follow-up

Out of the original forty patients in our previous investigations (Van den Heuvel et al., 2013; Collin et al., 2014), thirty were reassessed after 3 years (T-FU) and ten were lost to follow-up (see Supplementary material for details). There were no significant differences in clinical or MRI

measures between subjects that were lost to follow-up, relative to those reevaluated at T-FU (Supplementary material).

On average, patients showed more clinical symptoms as measured by PANSS total symptoms at T-FU as compared to T-MRI ($p = 0.005$). Specifically, twenty patients showed no clinically relevant (Hermes et al., 2012) difference in total PANSS symptoms (±15 points), one patient showed a decrease of 24 points and nine patients showed a clinically significant increase (range 16–37 points) in total symptoms. On average, mean (SD) IQ was lower at T-FU—96.7 (16.4)—than at T-MRI—99.5 (15.0)—but this effect did not reach significance ($p = 0.09$). The effects were similar when all subjects at T-MRI ($N = 40$) were included.

Table 2 summarizes the characteristics of the subjects per GF trajectory group. The only significant difference in clinical measures was IQ at follow-up, which was higher in the group showing increased GF at T-FU as compared to T-MRI than in the other groups.

### 3.2. Longitudinal changes in functioning, symptoms and IQ

#### 3.2.1. General functioning

Examining connectome organization revealed a trend-level positive effect on longitudinal changes in GF of overall connectivity *S* ($p = 0.030$, not surviving FDR-correction; Fig. 3a and c) and GE ($p = 0.034$, non-FDR significant). No clear effect of overall clustering was observed ($p = 0.08$). Strength of rich club and local connections was positively ($p = 0.007$ and $p = 0.003$ respectively, FDR-significant) related to change in GF during follow-up, with a trend-level effect for feeder connections ($p = 0.037$, non-FDR significant), consistent with the overall effect of *S* (Fig. 3b and d). To examine the impact of *S* on these findings (Lynall et al., 2010; Scholtens et al., 2014), the proportion of connectivity per connection class (i.e., rich club, feeder, local) relative to overall *S* was examined in a post hoc analysis, revealing only rich club connectivity to to be independently associated with longitudinal change in GF ($p = 0.030$; Fig. 3e), such that, independent of overall connectivity (*S*), greater rich club connectivity was associated with positive changes in general functioning during follow-up and vice-versa.

#### 3.2.2. Robustness of general functioning findings

Post hoc analyses were performed to assess the robustness of the findings on general functioning (see Supplementary material for details). First, distinguishing three trajectories of GF change (increase, stable, decrease)—i.e., including two patients with a major decrease in functional outcome in one larger group of all patients with decreased GF—confirmed the main finding ($p = 0.018$). Second, excluding patients with other than formal schizophrenia diagnosis (DSM 295.10; 295.30; 295.60; 295.90) did not change the association between rich club connectivity and general functioning change ($p = 0.024$). Third, excluding patients with GF level 0 at baseline ($N = 3$), to eliminate a possible floor effect, did not alter the main effect ($p = 0.011$). Fourth, correcting for dosage of antipsychotic medication and cannabis abuse/dependency through linear regression analysis did not change the main finding ($p = 0.019$).

#### 3.2.3. Clinical symptoms and IQ

Longitudinal changes in total PANSS symptoms and IQ were significantly associated with *C*, such that a less clustered connectome at T-MRI predicted subsequent increases in symptoms ($r = -0.46$, $p = 0.013$, FDR-significant) and decreases in IQ ($r = 0.54$, $p = 0.003$, FDR-significant) and vice-versa (Fig. 4). These effects remained highly significant when total IQ and symptoms at T-MRI were included as predictors ($p = 0.001$ and $p = 0.001$ respectively). Moreover, the effect with IQ change remained significant when controlling for overall connectivity ($p = 0.016$). In addition, trend-level effects (all not surviving FDR-correction) were observed between symptom change and *S* ($p = 0.030$), and IQ change and *S* ($p = 0.031$) and GE ($p = 0.026$). There were no significant cross-sectional associations between network measures and baseline symptoms and IQ (all $p > 0.25$, see Supplementary material). A post hoc analysis revealed the correlation between *C* and symptom change to be driven mainly by disorganization symptoms (Supplementary material). Notably, controls and siblings showed no significant correlations between longitudinal changes in subclinical symptoms and IQ, and measures of connectome organization (Supplementary material).

## 4. Discussion

Structural connectome wiring was examined in relation to longitudinal changes in general and intellectual functioning and clinical symptoms in 3 years following MRI assessment in a cohort of chronically ill schizophrenia patients. Examining patients' functioning over time

**Table 2**
Characteristics of subjects grouped by trajectory of change in general functioning (GF) during follow-up.

| | Increased outcome ($N = 5$) | | Stable outcome ($N = 12$) | | Decreased outcome (minor) ($N = 11$) | | Decreased outcome (major) ($N = 2$) | | P | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Scan | FU | Scan | FU | Scan | FU | Scan | FU | S | FU |
| Age at scan, mean (SD) | 29.4 (4.9) | | 33.3 (7.6) | | 29.0 (5.2) | | 26.5 (2.1) | | .36 | |
| Gender, M/F | 5/0 | | 10/2 | | 10/1 | | 2/0 | | .71 | |
| Duration of illness at T-MRI, mean (SD) | 7.5 (5.4) | | 8.1 (2.9) | | 9.1 (5.1) | | 4.1 (1.1) | | .44 | |
| DSM-diagnosis | | | | | | | | | .77 | .13 |
| Schizophrenia, *N* (%) | 4 (80) | 4 (80) | 8 (66.7) | 7 (58.3) | 10 (90.9) | 11 (100) | 2 (100) | 2 (100) | .45 | .08 |
| Schizoaffective disorder, *N* (%) | 1 (20) | 0 (0) | 3 (25) | 3 (25) | 1 (9.1) | 0 (0) | 0 (0) | 0 (0) | .68 | .17 |
| Other schizophrenia spectrum, *N* (%) | 0 (0) | 0 (0) | 1 (8.5) | 2 (16.6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | .67 | .36 |
| Bipolar disorder, *N* (%) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | .16 |
| IQ, mean (SD) | 111.8 (14.8) | 115.8[#] (10.3) | 97.8 (12.3) | 91.7 (12.7) | 96.6 (17.1) | 94.7 (17.6) | 95.0 (11.3) | 87.0 (11.3) | .30 | .04 |
| PANSS symptoms | | | | | | | | | | |
| Total, mean (SD) | 40.0 (8.0) | 43.0 (7.5) | 47.2 (10.2) | 60.9[*] (16.1) | 47.8 (14.9) | 55.9 (14.2) | 47.5 (6.4) | 64.5 (7.8) | .50 | .15 |
| Positive scale, mean (SD) | 9.6 (3.6) | 10.0 (1.9) | 10.2 (2.5) | 14.0[*] (4.5) | 10.8 (5.7) | 13.7 (5.2) | 10.0 (1.4) | 17.0[*] (1.4) | .84 | .26 |
| Negative scale, mean (SD) | 10.4 (3.4) | 11.0 (2.9) | 12.5 (3.6) | 16.8 (6.7) | 12.4 (3.2) | 14.8 (3.9) | 13.5 (2.1) | 15.5 (2.1) | .60 | .24 |
| General scale, mean (SD) | 20.0 (4.1) | 22.0 (5.4) | 24.5 (5.2) | 30.2 (8.6) | 24.6 (7.5) | 27.4 (8.1) | 24.0 (2.8) | 32.0 (4.2) | .45 | .22 |
| Antipsychotic medication | | | | | | | | | | |
| Clozapine/other atypical[a] /typical/none | 0/4/0/1 | 0/4/0/1 | 5/5/1/0[c] | 5/5/1/0[c] | 1/10/0/0[c] | 2/9/0/0[c] | 0/2/0/0 | 0/2/0/0 | .23 | .42 |
| CPZ[b] dose, mean (SD) | 200.0 (0.0) | 138.3 (73.7) | 296.2 (191.2) | 243.3 (159.0) | 247.3 (113.9) | 369.3 (279.2) | 200.0 (0.0) | 133.3 (0.0) | .93 | .06 |

[a] Atypical antipsychotics other than clozapine include risperidone, olanzapine, quetiapine and aripiprazole.
[b] CPZ = chlorpromazine.
[c] Data missing for $N = 1$.
[#] Group with increased GF at follow-up differs from other groups.
[*] Significant change between assessments.

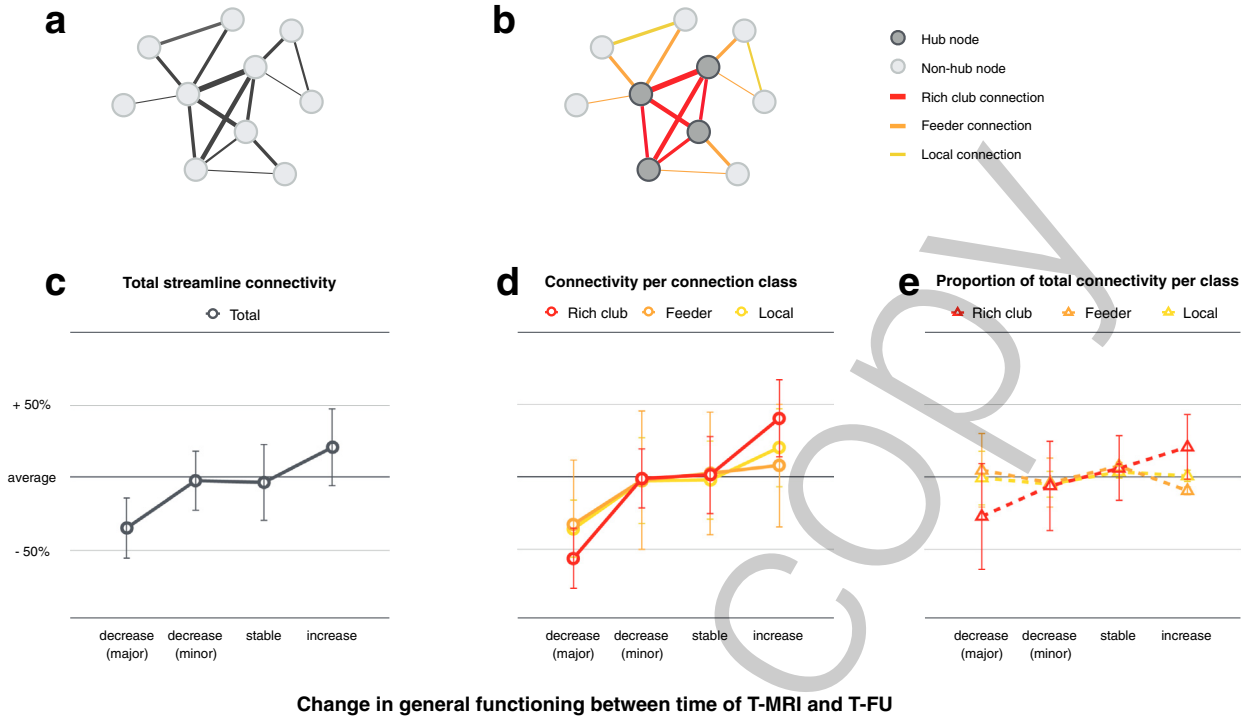


**Fig. 3.** Overall connectivity *S* (a) and connection classes (rich club, feeder and local connections) (b) were examined for a link with change in general functioning (GF) during follow-up. Total connectivity showed a trend-level effect with subsequent change in GF (c); rich club and local connectivity both showed significant associations (d), but only rich club connections remained significantly associated with GF change when examined as a proportion of *S* (e).

revealed more severely affected wiring of the connectome—especially concerning rich club connections—to precede a progressive decrease in functional performance over time, while relative sparing of these connections preceded stable or improved general functioning. Moreover, stronger alterations in global connectome topology—network clustering in particular—were shown to herald subsequent increases in total symptoms and decline in intellectual function, independent of baseline measures. Finding no such associations with change in IQ and subclinical symptoms in controls and unaffected siblings suggests that the findings in patients represent effects of ongoing illness, as opposed to normal age-related changes. Our findings are thus indicative of potential predictive value of connectome structure on illness progression in schizophrenia.

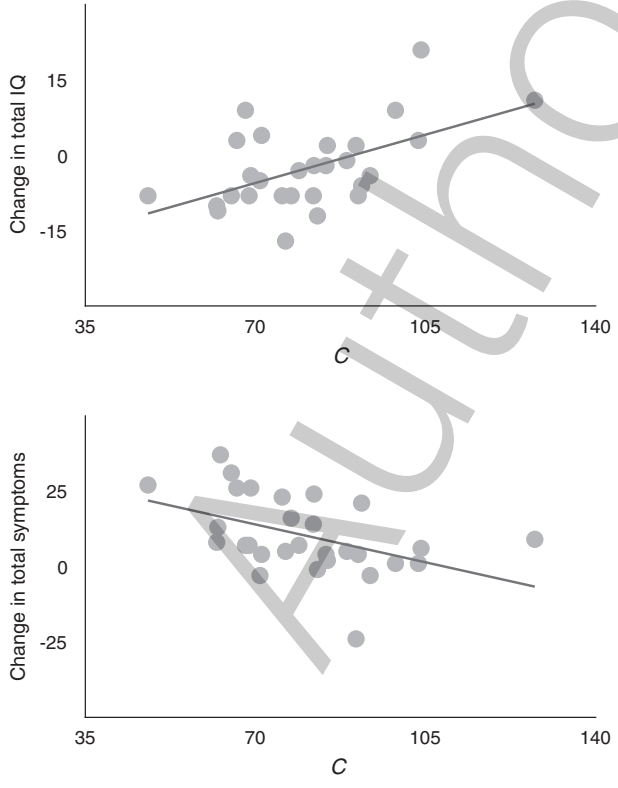


**Fig. 4.** Associations between connectome clustering *C* at T-MRI and subsequent changes in IQ (top) and total PANSS symptoms (bottom) during follow-up.

Abnormalities in connectome and rich club organization were previously shown to be present at intermediate levels in unaffected siblings of schizophrenia patients (Collin et al., 2014). This suggests that connectome alterations may reflect a neurodevelopmental insult or aberration of brain maturation (Fornito et al., 2012; Collin and van den Heuvel, 2013; Van den Heuvel and Fornito, 2014) related to familial, possibly reflecting genetic (Terwisscha van Scheltinga et al., 2013), factors. If connectome abnormalities are neurodevelopmental in nature, an explanation for our current findings might be that more affected connectome structure reflects a more severe phenotype that is associated with a higher probability of functional deterioration over time. In addition, a less efficiently wired connectome might be more susceptible for progressive white matter deterioration, which could in turn give rise to more severe functional decline. Indeed, theories of schizophrenia have characterized the illness as a progressive neurodevelopmental disorder, implying a pathogenic process that begins in early neurodevelopment, evolves until it reaches a critical threshold and subsequently causes progressive brain decline (Woods, 1998; Swapnil and Kulhara, 2010; Rapoport and Gogtay, 2011). Brain hubs may be pertinent in this respect as their topological centrality may make them vulnerable to pathogenic factors, rendering hubs a 'hot spot' for (progressive) neural changes (Van den Heuvel and Sporns, 2013; Crossley et al., 2014). Our current finding that the level of connectivity among brain hubs best predicted progressive changes in real-world functioning adds that this central infrastructure may be crucial to illness progression. Longitudinal studies

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examining possible progressive changes in connectome and hub wiring over time are needed to provide more insight in this matter.

The current study examined connectome organization in relation to longitudinal changes in functional and clinical outcome in chronic schizophrenia. While the greatest changes in brain measures and functioning presumably occur in earlier stages of illness, brain tissue continues to decline in the chronic phase (Hulshoff Pol and Kahn, 2008), and so do social (Martin et al., 2015) and certain neurocognitive functions (Jahshan et al., 2010; Zanelli, 2012; Barder et al., 2013; Thompson et al., 2013). Moreover, cognitive trajectories appear to be heterogeneous across individual patients (Barder et al., 2013; Thompson et al., 2013) and cognitive domains (Jahshan et al., 2010), with some improving with stabilization in the early stages while others decline with progressing illness. In addition, ongoing brain changes until 12 years after first diagnosis have been shown to correlate with functional outcome (Ho et al., 2003). In all, changes in functioning occur in advanced illness, in diverging trajectories, and are related to ongoing brain changes. Our study extends these findings by suggesting that brain network organization may be predictive of subsequent changes in outcome some years after first diagnosis, at which time patients may question their future perspective in terms of symptoms and functioning, for example, in relation to study or work.

With regard to predicting outcome, previous investigations of first-episode (Van Veelen et al., 2011) and chronic (Khodayari-Rostamabad et al., 2010) schizophrenia patients have shown that functional MRI and EEG measurements may be useful in anticipating treatment response. In addition, consistent with our findings, reduced volumes of dorsolateral prefrontal and superior frontal cortices were demonstrated to predict worse socio-occupational functioning (Prasad et al., 2005; Behere, 2013), more negative symptoms (Behere, 2013) and to differentiate between poor and good functioning patients at follow-up (Kasparek et al., 2009). In addition, fronto-parietal components of functional brain networks were reported to contain the most predictive information regarding later improvement in negative symptoms (Nejad et al., 2013). In all, brain (network) measures relating to frontal brain hubs and their connections to other hub regions of the brain may include useful new metrics to inform prognostic estimations in schizophrenia (Van den Heuvel and Kahn, 2011).

Studies examining individuals at clinical or genetic high risk for psychosis have shown that neurophysiological, neurochemical and neurostructural markers can be used to predict subsequent symptom progression (Tognin et al., 2013), transition to psychosis (Howes et al., 2011; Mechelli et al., 2011; Allen et al., 2012) and functional outcome (Allen et al., 2014) in these individuals. In this context, a worthwhile avenue for future research may be to examine whether measures of brain network organization are also predictive of future functioning in the first-episode, or in high-risk individuals.

Our findings are limited by the inherent nature of the applied methodology. Limitations associated with diffusion-weighted imaging, a technique that relies on water diffusion as an indirect marker for axon geometry, include difficulties in resolving complex fiber architecture, such as crossing, diverging or converging fibers (for a review, see Jbabdi and Johansen-Berg, 2011). In addition, the majority of patients in this study used antipsychotic medication, which may influence structural brain connectivity (Szeszko et al., 2014). However, in this context, it should be noted that altered white matter connectivity has also been shown in medication-naïve patients (Cheung et al., 2008; Mandl et al., 2013), and in our current study population, no clear influence of the chlorpromazine equivalent dosage of antipsychotic treatment on connectome measures was observed (Collin et al., 2014), nor on the relationship with longitudinal changes in general functioning, as examined here.

This study provides evidence that connectome and rich club organization may be predictive of illness progression, including longitudinal changes in general functioning, clinical symptoms and IQ, in chronically ill schizophrenia patients. These findings highlight the potential of connectome measures in informing prognosis in schizophrenia.

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The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

**Contributors**

Authors WC and JdN were responsible for data collection. Authors GC and MPvdH designed the study and analyzed the data. Author GC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

**Conflict of interest**

The authors report no conflict of interest.

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## Appendix A. Supplementary data

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