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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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