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Grey matter networks in people at increased familial risk for schizophrenia

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ABSTRACT

Grey matter brain networks are disrupted in schizophrenia, but it is still unclear at which point during the development of the illness these disruptions arise and whether these can be associated with behavioural predictors of schizophrenia. We investigated if single-subject grey matter networks were disrupted in a sample of people at familial risk of schizophrenia.

Single-subject grey matter networks were extracted from structural MRI scans of 144 high risk subjects, 32 recent-onset patients and 36 healthy controls. The following network properties were calculated: size, connectivity density, degree, path length, clustering coefficient, betweenness centrality and small world properties.

People at risk of schizophrenia showed decreased path length and clustering in mostly prefrontal and temporal areas. Within the high risk sample, the path length of the posterior cingulate cortex and the betweenness centrality of the left inferior frontal operculum explained 81% of the variance in schizotypal cognitions, which was previously shown to be the strongest behavioural predictor of schizophrenia in the study. In contrast, local grey matter volume measurements explained 48% of variance in schizotypy.

The present results suggest that single-subject grey matter networks can quantify behaviourally relevant biological alterations in people at increased risk for schizophrenia before disease onset.

1. Introduction

It is generally accepted that people with established schizophrenia have abnormalities in their grey matter structure, as measured with structural magnetic resonance imaging (MRI) (Lawrie and Abukmeil, 1998; Wright et al., 2000). Several studies have investigated whether such structural changes may be detectable in their relatives, even if only to a lesser extent. One of the aims of the Edinburgh High Risk Study of Schizophrenia (EHRS) is to find such biological risk factors for the illness in people at increased familial risk (Hodges et al., 1999; Johnstone et al., 2000; Johnstone, 2005; Lawrie et al., 2007).

Thus far, the EHRS and other familial high risk studies have found disruptions in grey matter volume, thickness and folding between high risk subjects and healthy controls (Boos et al., 2011; Cannon et al., 1998; Diwadkar et al., 2006; Job et al., 2003; Lawrie et al., 1999; Rosso et al., 2010; Sprooten et al., 2013; Suddath et al., 1990). Increased rates of grey matter volume change have also been reported in high risk subjects who later developed schizophrenia (Job et al., 2005; Mcintosh et al., 2011). Still, it remains largely unclear as to what extent these abnormalities predict disorder, and whether they differ between those high risk individuals who will develop symptoms and those who will remain asymptomatic. Identifying such temporal dynamics is pivotal for distinguishing the biological causes of the disease from its consequences, medication effects and the genetic background that may be non-causal to the disorder per se.

Graph theory has recently been used to investigate brain networks that are based on covariance of grey matter volume or thickness between cortical areas across individuals (Alexander-Bloch et al., 2013a; Evans, 2013; Mechelli et al., 2005). Brain areas that correlate in size are often implied in sub-networks that underlie specific cognitive functions (Amunts et al., 1997; Bailey et al., 2014; Maguire et al., 2000). For example, brain areas that are involved in visual processing, grow in a coordinated way (Andrews et al., 1997; Voss and Zatorre, 2015). Such coordinated grey matter growth has been associated with functional coactivation during development (Alexander-Bloch et al., 2013b; Draganski et al., 2004; Liao et al., 2013), axonal connectivity (Gong et al., 2012) and genetic factors (Schmitt et al., 2008, 2009). Brain networks have been robustly characterised by specialised sub-networks

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of densely interconnected brain areas (i.e., clustering) and information can be integrated between clusters via sparse, long-range connections that reduce the average path length between any two brain areas (Alexander-Bloch et al., 2013a; Bassett and Gazzaniga, 2011; Bullmore and Sporns, 2012; Evans, 2013; Sporns et al., 2004); a property that is also known as 'small world' (Watts and Strogatz, 1998). In schizophrenia grey matter networks are disorganised (Bassett et al., 2008; Collin et al., 2013; Shi et al., 2012; Zhang et al., 2012; for reviews see: van den Heuvel and Fornito, 2014; Rubinov and Bullmore, 2013; Xia and He, 2011). It remains unclear, however, at what point during the development of schizophrenia these disruptions arise and if they can be related to behavioural predictors of the illness.

Recently, we have proposed a method to construct single-subject grey matter networks (Tijms et al., 2012, 2013, 2014). Presently, we investigated whether grey matter networks show disruptions in people at increased familial risk for schizophrenia. Networks of recent-onset schizophrenia patients were also analysed as an aid for the interpretation of the results. Finally, we examined if network property values were related to scores on the Rust Inventory of Schizotypal Cognitions, which was the strongest behavioural predictor of schizophrenia in the EHRS (Johnstone, 2005).

2. Materials and methods

2.1. Ethics statement

All patients, relatives, and control subjects gave written informed consent to their participation. The study as a whole was approved by the Lothian Health Board Research Ethics Committee, and was conducted according to national guidelines on the ethical conduct of research that conformed to the Declaration of Helsinki.

2.2. Study participants

High risk participants were identified throughout Scotland on the basis that they had at least two first- or second-degree relatives affected with schizophrenia and that they themselves had no personal history of psychiatric disorders (Hodges et al., 1999). This was done through examination of the case notes of all patients with schizophrenia known to individual hospitals. In the case it appeared that a patient had a close relative who was also affected with schizophrenia, consent was sought from the patient to contact a healthy relative. From this relative the possibility of there being a close relative aged 16–24 years was explored, and such young family members were generally contacted through an older healthy relative. At the start of the study none of the high risk participants was diagnosed with schizophrenia. Healthy controls were recruited from the social networks of the high risk subjects and recent-onset schizophrenia patients from local hospitals. In total 220 EHRS participants underwent a structural MRI at baseline (i.e., the first round of scans before any of the participants were ill). During the EHRS study, psychopathology was assessed at approximately 18-month intervals for up to 10 years between 1994 and 2004 with the Present State Examination (Wing et al., 1974) and any diagnoses were made based on the data obtained at these interviews (Johnstone, 2005). Seventy-two high risk subjects never experienced psychotic symptoms during the period of the study (HR_W), 55 subjects experienced symptoms at some point during the study but did not develop schizophrenia (HR_S) and 17 subjects developed schizophrenia (HR_I; on average after 2.5 years). None of the high risk subjects were treated with antipsychotic drugs at any point during the study. Twenty recent-onset schizophrenia patients were prescribed first generation antipsychotic drugs, 10 patients were on atypical antipsychotics and 2 were unmedicated. The present study included participants' scores on the Rust Inventory of Schizotypal Cognitions (RISC, i.e., a self-completed questionnaire on schizotypal features; Rust, 1988). The RISC is a measure of personality, which was assessed at the baseline of the study. More details about the EHRS have been described in our earlier papers (Hodges et al., 1999; Johnstone et al., 2000; Johnstone, 2005).

2.3. Scan acquisition and preprocessing

Participants were scanned in a 1 Tesla 42 SPE Siemens (Erlangen, Germany) Magneton. T1 weighted scans were acquired with a three-dimensional Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TR = 10 ms, TE = 4 ms, TI = 200 ms, relaxation delay time 500 ms). Full details of scan acquisition are described in Job et al. (2003). Scans were phantom corrected and preprocessed with the use of the Statistical Parameter Mapping software version 8 (SPM8) running in MATLAB version 7.3.0.298 R2006b (The Mathworks, Natick, MA, USA) with the use of the default parameters. At this point 8 EHRS scans could not be used for further analysis (3 showed gross lesions, 5 were lost to technical malfunctions). Native space grey matter segmentations were resliced with a voxel size of 2 mm^3 isotropic using nearest neighbour interpolation. 90 anatomical areas were identified with the use of the Automated Anatomical Labelling Atlas (AAL; Tzourio-Mazoyer et al., 2002) and the Individual Brain Atlases Statistical Parametric Mapping (IBASPM) toolbox in SPM8. This toolbox was also used to obtain native space measurements of whole brain and regional grey matter volumes.

2.4. Extraction of networks and computation of network properties

Single-subject grey matter networks were constructed with a completely automated and data-driven method (https://github.com/bettytijms/Single_Subject_Grey_Matter_Networks; Tijms et al, 2012). Fig. 1 provides a schematic overview of this method. Briefly, the nodes were defined as small regions of interest of $6 \times 6 \times 6$ mm^3 (encompassing 27 voxels) using a template that minimised the number nodes, while covering all grey matter voxels. The size of the regions of interest were chosen so that the size of networks were maximised (to generate stable network statistics) and could still capture cortical thickness and folding (Kiselev et al., 2003). Nodes were connected with edges when they showed similar grey matter structure as determined by the correlation coefficient. The similarity matrices were binarised after determining a threshold with a random permutation method to ensure for all subjects a similar chance of including 5% spurious correlations in the networks (Noble, 2009).

For each network the following global (i.e., at the network level) and local (i.e., at the nodal level) properties were computed: the size (i.e., the number of nodes), global and local degree (i.e., average number of edges per node), the connectivity density (i.e., the percentage of existing edges out of the total number of possible edges), global and local clustering coefficient C (i.e., the level of interconnectedness between neighbouring nodes), global and local characteristic path length L (i.e., the minimum number of edges to traverse between any two nodes), global and local betweenness centrality BC and the small world coefficient. The small world coefficient was computed by normalising the average clustering coefficient and average characteristic path length with the average values calculated from 20 random networks that kept intact the degree distribution. Local properties were averaged across the nodes within each of the 90 anatomical areas for between subject comparisons. Network analyses were performed with in-house software and modified scripts from the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) implemented in Matlab v7.

2.5. Statistical analyses

Statistical comparisons were performed in R version 2.15.0. Some network properties deviated from normality as tested with Kolmogorov–Smirnov normality tests (as implemented in R package "nortest"). Rank transformation of network property values was applied when more advanced parametric analysis methods were required

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