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An affected core drives network integration deficits of the structural connectome in 22q11.2 deletion syndrome

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ABSTRACT

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic disease known to lead to cerebral structural alterations, which we study using the framework of the macroscopic white-matter connectome. We create weighted connectomes of 44 patients with 22q11DS and 44 healthy controls using diffusion tensor magnetic resonance imaging, and perform a weighted graph theoretical analysis. After confirming global network integration deficits in 22q11DS (previously identified using binary connectomes), we identify the spatial distribution of regions responsible for global deficits. Next, we further characterize the dysconnectivity of the deficient regions in terms of sub-network properties, and investigate their relevance with respect to clinical profiles. We define the subset of regions with decreased nodal integration (evaluated using the closeness centrality measure) as the affected core (A-core) of the 22q11DS structural connectome. A-core regions are broadly bilaterally symmetric and consist of numerous network hubs — chiefly parietal and frontal cortical, as well as subcortical regions. Using a simulated lesion approach, we demonstrate that these core regions and their connections are particularly important to efficient network communication. Moreover, these regions are generally densely connected, but less so in 22q11DS. These specific disturbances are associated to a rerouting of shortest network paths that circumvent the A-core in 22q11DS, "de-centralizing" the network. Finally, the efficiency and mean connectivity strength of an orbito-frontal/cingulate circuit, included in the affected regions, correlate negatively with the extent of negative symptoms in 22q11DS patients, revealing the clinical relevance of present findings. The identified A-core overlaps numerous regions previously identified as affected in 22q11DS as well as in schizophrenia, which approximately 30–40% of 22q11DS patients develop.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic disease affecting 1 in 4000 live births (Scambler, 2000), and generally caused by a 1.5–3 megabase deletion on the long arm of chromosome 22 (Lindsay et al., 1995). As approximately 30–40% of 22q11DS patients develop schizophrenia spectrum disorders during adulthood and even more will experience psychotic symptoms during their lifetime (Murphy et al., 1999; Monks et al., 2014; Schneider et al., 2014a), the 22q11.2 microdeletion has become an established genetic model for schizophrenia spectrum disorders.

Patients with 22q11DS exhibit overall reductions in brain volume and morphological abnormalities. While gray matter alterations include loss of volume (Shashi et al., 2010), cortical thickness (Bearden et al., 2009; Jalbrzikowski et al., 2013) and gyrification (Schaer et al., 2006, 2009), white matter deficits appear both more extensive and more diffuse (Barnea-Goraly et al., 2003; Simon et al., 2005). Specifically, volumetric analyses reported decreases in white matter volume in parietal, temporal (Kates et al., 2001) and frontal lobes (Campbell et al., 2006). Moreover, numerous studies used diffusion tensor imaging (DTI) to report deficits in white matter integrity in the same regions (Barnea-Goraly et al., 2003; Simon et al., 2008; Sundram et al., 2010; Kikinis et al., 2012; Jalbrzikowski et al., 2014), in the corpus callosum and midline structures (Simon et al., 2005), in tracts to and from all cerebral lobes (Radoeva et al., 2012) as well as within and between limbic structures and fronto-temporal regions (Ottet et al., 2013a). Together with gray matter abnormalities, these extensive, diffuse white matter

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alterations may be responsible for disruptions in brain function (Debbané et al., 2012; Rihs et al., 2013; Scariati et al., 2014; Schreiner et al., 2014; Tomescu et al., 2014) and cognitive deficits (Glaser et al., 2007; Dufour et al., 2008).

Diffuse and distributed diseases such as 22q11DS are suited for analysis using the framework of the structural magnetic resonance connectome, a holistic description of the brain's macroscopic connectivity (Hagmann, 2005; Sporns et al., 2005). A structural magnetic resonance connectome is a complex network, where nodes correspond to gray matter regions, while edges capture white matter connectivity between them. In binary networks, edges only indicate the presence of connections between regions. Conversely, weighted networks capture the relative importance of network connections. Various magnetic resonance measures of diffusivity or myelination can be used to quantify edge importance, reflecting diverse properties of the underlying white matter substrate (Hagmann et al., 2010).

The mathematical framework of graph theory can be applied to connectomes to characterize organizational principles of brain network connectivity in health and their breakdown in disease (Hagmann et al. 2008; Bullmore and Sporns, 2009). This framework has been applied to numerous pathologies (Griffa et al., 2013; Rubinov and Bullmore, 2013), including schizophrenia (van den Heuvel et al., 2010; Zalesky et al., 2011; Fornito et al., 2012; Wang et al., 2012a; van den Heuvel and Fornito, 2014) and 22q11DS (Ottet et al., 2013b).

The first study to apply graph theory to binary connectomes of 22q11DS patients reported deficits in topological integration and an involvement of important "hub" nodes in the disease. Moreover, it demonstrated associations between individual hallucination scores and the local efficiency of several regions hypothesized to be involved in causing hallucinations (Ottet et al., 2013b). However, the subset of regions responsible for global differences in integration was not pinpointed, or studied.

Graph theoretical measures of global connectivity can be sensitive to connectivity alterations in disease, although their specificity is impeded by the potential of different diseases to affect global brain topology in similar ways (Griffa et al., 2013; Rubinov and Bullmore, 2013). At the local level, disease-specific dysconnectivity has been studied using nodal graph-theoretical measures (e.g., van den Heuvel et al., 2010; Ottet et al., 2013b; see also Griffa et al., 2013), as well as statistical methods designed to identify network components (Zalesky et al., 2010; Meskaldji et al., 2011) or individual edges and nodes (Meskaldji et al., 2015) with reduced connectivity strength. However, the dysconnectivity of sub-networks responsible for deficits in higher-order network properties such as integration or segregation has, until recently (Griffa et al., 2015), not been studied.

In this study, we use weighted network analysis to confirm findings of deficits in global integration in 22q11DS, previously reported in an overlapping sample of participants using binary connectomes (Ottet et al., 2013b). In addition, we extend previous findings of 22q11DS dysconnectivity by identifying and studying the spatial distribution of regions driving the global integration differences, referred to as the "affected core" (A-core). We demonstrate that these core regions and their connections are particularly important to efficient network communication, describe their role in disrupting communication efficiency in the 22q11DS connectome and identify network alterations related to negative symptoms in 22q11DS.

2. Methods

2.1. Participants

Forty-four participants with 22q11DS aged between 13.1 and 31.5 years (median(inter-quartile range) = 18.2(5.9) years) participated in the study. The chromosome 22q11.2 deletion was confirmed by analysis of a blood sample with the Quantitative Fluorescent Polymerase Chain Reaction.

Forty-four healthy participants aged between 13.1 and 30.4 years (median(inter-quartile range) = 17.8(6.2) years) served as controls. None of the control participants had a history of psychiatric or neurological disorders. Subjects were matched for age (two-tailed Wilcoxon rank-sum test (WRST), $p = 0.65$) and gender, each group consisting of 23 females and 21 males.

Participants' IQ was assessed using Wechsler intelligence scales — WISC-III for children under 17 years (Wechsler, 1991) and WAIS-III for older participants (Wechsler, 1997). There were significant differences in full-scale IQ between 22q11DS patients (median(inter-quartile range) = 69.5(17)) and healthy participants (median(inter-quartile range) = 107.5(18)) (two-tailed WRST, $p < 0.001$).

22q11DS patients completed the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991), which assesses the presence of symptoms from positive (e.g., hallucination or delusion), negative (e.g., social withdrawal or blunted affect) and disorganized (e.g., odd speech and behavior) dimensions. The medians(inter-quartile ranges) on the SPQ were respectively: Total Score — 20(27.5), Positive — 6(12), Negative — 5(10) and Disorganized — 9(6). Moreover, the presence of psychiatric disorders was evaluated using the Diagnostic Interview for Children and Adolescents — Revised (DICA-R; Reich, 2000) for adolescents under 18 years, and using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I; First et al., 1996). Of the sample of 44 22q11DS patients, 7 were diagnosed with psychosis (15.9%) and 2 with schizophrenia (4.6%).

At the time of testing, 17 (38.6%) patients were receiving psychotropic medication: 7 (15.9%) were on methylphenidate, 6 (13.6%) on antidepressants, 5 (11.4%) on antipsychotics, 4 (9.1%) on anticonvulsants and 1 (2.3%) on anxiolytics.

Written informed consent was obtained from all participants or their parents. The institutional review board of Geneva University School of Medicine approved the study protocol. Of the present 88 participants, 56 (63.6%) were included in a related recent study by Ottet et al. (2013b). The present sample also overlaps other (less directly relevant) recent studies on magnetic resonance imaging structural or functional connectivity in 22q11DS. Specifically, these are studies on structural connectivity (without graph-theoretical analysis) (Ottet et al., 2013a), resting-state functional connectivity (Debbané et al., 2012; Scariati et al., 2014) and structural and functional connectivity within the default mode network (Padula et al., 2015). For detailed quantitative information on sample overlaps, see supplementary table S1.

2.2. Image acquisition and preprocessing

Magnetic resonance imaging (MRI) was performed using a Siemens 3T MRI scanner, including an anatomical T1-weighted scan and a DTI scan (30 directions, maximum b-value 1000 s/mm^2). Individual connectomes were created using the Connectome Mapping ToolKit (Daducci et al., 2012), which combines several MRI processing programs into an integrated pipeline. First, T1-weighted volumes were registered to DTI data (Jenkinson et al., 2002). FreeSurfer was applied to registered T1-weighted volumes to remove non-brain tissue and segment remaining tissue into gray and white matter (Fischl et al., 2002). Subsequently, gray matter was parcellated into 82 cortical and subcortical regions of interest (ROIs). DTI data was realigned and corrected for effects of head motion (Jenkinson et al., 2002). Next, deterministic streamline tractography was used within white matter to reconstruct macroscopic white matter tracts (Wang et al., 2007). Finally, overlap between streamlines and the ROI mask enabled the creation of individual structural connectomes. Acquisition and preprocessing details are described in the supplementary information.

2.3. Weighted connectome creation

As there is currently no consensus on how best to weight connectomes, we used several connectome weightings, to ensure