Title:
Large-scale functional network reorganization in 22q11.2 deletion syndrome revealed by modularity analysis

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Abstract:
The 22q11.2 deletion syndrome (22q11DS) is associated with cognitive impairment**s** and a 41% risk of developing schizophrenia. While several studies performed **on patients with** 22q11DS showed the presence of abnormal functional connectivity in **this** syndrome, how these alterations affect large-scale network organization is still unknown. Here we performed a network modularity analysis on whole-brain functional connectomes derived from the resting-state fMRI of 40 patients with 22q11DS and 41 healthy control participants, aged between 9 and 30 years old. We then split the sample at 18 years old to obtain two age subgroups and repeat**ed** the modularity analyses. We found alterations of modular communities affecting the visuo-spatial network and the anterior cingulate cortex (ACC) in both age groups. These results corroborate previous structural and functional studies in 22q11DS that showed early impairment of visuo-spatial processing regions. Furthermore, as ACC has been linked to the development of psychotic symptoms in 22q11DS, the early impairment of its functional connectivity provide further support that ACC alterations may provide potential biomarkers for an increased risk of schizophrenia. Finally, we **found** an abnormal modularity partition of the dorsolateral prefrontal cortex only in adults with 22q11DS, suggesting the presence of an abnormal development of functional network communities during adolescence in 22q11DS.

Keywords: *brain development, connectome, graph theory, modularity, resting-state fMRI, schizophrenia*

1. Introduction :

Patients with the 22q11.2 deletion syndrome (22q11DS) present cognitive impairments including mild intellectual disability and difficulties in visuo-spatial, executive and social tasks (Antshel et al., 2008; Shashi et al., 2012). The syndrome is also characterized by a 41% prevalence of schizophrenia spectrum disorders, which usually develop during adolescence (Schneider, Debbane, et al., 2014). Therefore 22q11DS is recognized as a genetic model for studying schizophrenia (Murphy et al., 1999). Neuroimaging studies have shown associations between brain connectivity alterations and the clinical and cognitive phenotype in 22q11DS. Indeed, diffusion tensor imaging (DTI) studies (reviewed in (Gothelf et al., 2008)) have reported relationships between microstructural irregularities of the white matter tracts and cognitive symptoms including arithmetic difficulties, and deficits in attention and social capacities (Barnea-Goraly et al., 2005; Radoeva et al., 2012; Simon et al., 2008). Similar alterations have been associated with the intensity of schizotypal traits (Sundram et al., 2010) and psychotic symptoms (Jalbrzikowski et al., 2014; Radoeva et al., 2012).

Brain connectivity is usually investigated in **functional magnetic resonance imaging (fMRI)** by recording brain function during a period of rest. **In resting-state fMRI, brain connectivity can be inferred from the temporal coordination of spontaneous activity in cortical and subcortical brain areas** (Biswal et al., 1995; E. Bullmore & Sporns, 2009). Functional brain networks, like many other real-world networks are organized in communities of strongly interconnected regions (also called modules) that support specific cognitive functions (Chen et al., 2008; He et al., 2009; Meunier et al., 2009; Meunier et al.,

2010; Schwarz et al., 2008). Such network organization has strong advantages as it enables locally specialized information processing and global integration at low wiring and energy costs (E. Bullmore & Sporns, 2009, 2012). Disruption of modular organization is associated with brain dysfunction and has been identified in several psychiatric (Barttfeld et al., 2011; Davis et al., 2013) and neurological (Baggio et al., 2014; Gamboa et al., 2014; Vaessen et al., 2013) disorders, including child-onset schizophrenia (A. Alexander-Bloch et al., 2013). To the best of our knowledge, only one study, previously published by our group, investigated the community partitioning of the functional brain network in 22q11DS (Debbane et al., 2012). **In this study, we** showed impairments in the default mode (DMN), visual processing and sensory-motor networks in adolescents with 22q11DS **using an Independent Component Analysis (ICA).** However, **by using** a temporal ICA **we obtained** resting-state networks that were **spatially similar in both groups (Calhoun et al., 2009).** Thereby, it is still unknown whether brain network communities are differently shaped in 22q11DS. This question can be answered using modularity algorithms, which provide group-specific modules that can subsequently be statistically compared (A. F. Alexander-Bloch et al., 2010; E. T. Bullmore & Bassett, 2011). Furthermore, this previous study was only performed on a subsample of our cohort **that was composed of** adolescents. Thus, brain network alterations in other age groups remain to be investigated.

Other papers **have** also investigated resting-state functional connectivity in 22q11DS. Two of them specifically focused on the DMN and confirmed the presence of an altered functional connectivity in this network (Padula et al., 2015; Schreiner et al., 2013). **Of** these two papers, one was performed on our same cohort of patients and showed a partial overlap between structural and functional alterations of DMN connectivity (Padula et al., 2015). The other was performed on an independent sample and showed a correlation between DMN dysconnectivity and social skills (Schreiner et al., 2013). A third paper, also published by our group, tested the whole brain functional connectomes and described the presence of widespread functional connectivity alterations in 22q11DS, particularly in the frontal lobe (Scariati et al., 2014). However, even though altered functional connectivity has been described in 22q11DS, it is still unclear how this dysconnectivity affects functional network organization. Furthermore, the evolution of the functional network with age remains largely unknown in this disorder. The two studies that focused on the DMN investigated the relationship between age and connectivity. **O**nly one of them **found** evidence for an abnormal development of resting-state connectivity in 22q11DS (Schreiner et al., 2013), while the other found no relationship between functional connectivity and age (Padula et al., 2015). **However**, evidence suggests the presence of an altered neurodevelopment in 22q11DS, (reviewed in (Gothelf et al., 2008)) particularly in frontal lobe gray matter (Schaer et al., 2009; Shashi, Veerapandiyan, Keshavan, et al., 2012). Given that specific resting-state connectivity patterns have been associated with the presence of psychotic symptoms **in this population** (Scariati et al., 2014), identifying early course brain connectivity alterations is crucial as they may carry predictive value for the development of schizophrenia and may therefore potentially act as a biomarker for **an** increased risk of psychosis.

In the present study, we investigated the specificities of resting-state networks modularity partitioning in a sample of patients with 22q11DS compared to healthy control participants aged from 9 to 30 years. Furthermore, we divided our sample into two age subgroups: one **included** children and adolescents from 9 to 18 years old**, the other included** the adults (≥18 years old). This cut off corresponds not only to the commonly admitted limit between adolescence and early adulthood, but also to the mean age of schizophrenia onset in patients with 22q11DS (Gothelf et al., 2013). This threshold was furthermore used in several previously published papers (Padula et al., 2015; Schaer et al., 2009; Schneider, Debbane, et al., 2014; Schneider, Schaer, et al., 2014), which makes the comparison of our results with previous literature on the topic much easier. We expect to find between-group differences in community partitioning, mainly located in regions overlapping with our previous ICA results (Debbane et al., 2012), namely in visuo-spatial processing networks and **the** DMN. Furthermore, we hypothesize that the brain networks will exhibit specific differences in children and adolescents relative to adults. For instance, we expected the parietal and occipital lobes to show early alterations, and the frontal lobe to be affected only in the adult group**. This** would be consistent with previous evidence of altered trajectories of frontal gray matter development (Schaer et al., 2009).

2. Material and Methods

2.1. Research protocol:

Our research protocol was approved by the Institutional Review Board of the Geneva University School of Medicine. It included clinical and cognitive assessment**s** performed by trained psychiatrists and psychologists, as well as magnetic resonance **imaging data** scanning. The intelligence quotient (IQ) was tested with the *Wechsler Intelligence Scale for Children* (3rd Edition revised, (Wechsler, 1991)) for participants up to the age of 17 years and with the *Wechsler Adult Intelligence Scale-III* (Wechsler, 1997) for older participants. In the patients group, the presence of schizophrenia was assessed using the *Diagnostic Interview for children and adolescents (DICA)* (Reich, 2000) for children and the *Structured Clinical Interview for DSM-IV AXIS I Disorders* (First, 1997) (SCID) for adults. Handedness was assessed with the Edinburgh questionnaire (Oldfield, 1971), a participant was considered right- or left-handed if he used that hand for more than 50% of his daily activities. All participants completed the psychotic disorders section of the K-SADS (Kaufman et al., 1997). Table 1 summarizes the demographic **information** for the different groups of our analyses.

2.2. Participants:

Patients with 22q11DS were recruited through family associations in French and English speaking countries in Europe. Blood samples were collected for all participants and the presence of the deletion was confirmed with a Polymerase Chain Reaction (PCR) test. For this study, resting-state and structural data **was acquired from** 69 patients. We used the same exclusion criteria detailed in our previous paper (Scariati et al., 2014) resulting in the exclusion of a total of 22 scans: 18 scans were excluded for excessive motion (>3mm translation or 3° rotation), 2 scans due to a part of the brain not being in the field of view (FOV) and 2 scans due to the participants falling asleep during the resting-state

acquisition. In addition to the previous criteria, compared to our former study we also computed the Framewise Displacement (FD), which measures the amount of relative motion along the functional scanning session (Power et al., 2012; Van Dijk et al., 2012) and provides more strict control for motion confounds. Among the subjects that were not excluded from the analysis, we matched the groups for gender, age and FD in order to avoid any significant differences across these measures. In the end, the patients group comprised 40 participants (19 females) aged between 9 and 30 years.
The control group was initially composed of 51 healthy controls with the same age range as the patient group. Control participants were either recruited through announcements in the community and public schools or were the healthy siblings of patients. Participants with past or current history of neurological or psychiatric diseases were excluded. In this group, a total of 6 scans had to be excluded: 4 scans due to excessive motion and 2 because the full brain was not in the FOV. After matching with the patient group, the healthy control group was composed of 41 participants (21 females). Among them, 21 had a sibling with the 22q11DS from which 14 had their own sibling included in the patients group. All the analyses were recomputed after removing the healthy control participants that had a sibling in the patients' group. Only the results that were different after **the removal of the siblings** were reported in the Results section, however complete results for these additional recomputed analyses can be found in the Supplementary Material.

There were no between-group significant differences in gender, age, motion regressors (all 6 measurements) or mean FD (all $p>0.2$ uncorrected), however, the FSIQ was significantly lower in patients (T-Test p value <0.001). Table 1 details the demographic characteristics for these groups. Part of this sample was included in three previous papers from our group: 17 healthy control participants (9 females) and 17 patients with 22q11DS (8 females) were part of (Debbane et al., 2012); 27 control participants (18 females) and 26 patients (15 females) were included in (Padula et al., 2015); and all the participants except five control participants (2 females) and five patients (4 females) were included in our previous paper (Scariati et al., 2014).

2.3. Imaging:

2.3.1. Acquisition parameters:

The scanning sessions were performed at the Center for Biomedical Imaging (CIBM) in Geneva (Switzerland) on a Siemens Trio 3T with a 16-channel receiver head coil. The anatomical T1 weighted sequence comprised 192 contiguous coronal slices (voxel size: 0.86x0.86x1.1mm, TR: 2500ms, TE: 3ms, flip angle: 8°). The 8 minutes resting state sequence **comprised** 200 volumes of blood-oxygen-level dependent images (38 axial slices, voxel size: 1.84x1.84x3.2mm; TR: 2400ms; TE: 30ms; flip angle: 85°). During this acquisition the participants were instructed to **relax, not to fall asleep, and to concentrate on** a white cross, projected **at the center of a dark background**. In order to avoid excessive head motion, the head was stabilized with material adapted to the participants' morphology.

2.3.2. Preprocessing and computation of the connectivity matrices:

The images were preprocessed using Statistical Parametric Mapping 8 (SPM8 Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm/) and the open-source "connectivity decoding toolkit" (http://web.stanford.edu/~richiard/software.html) to obtain functional connectivity matrices as described in previous work (Richiardi et al., 2011; Scariati et al., 2014). More specifically, the functional images were realigned to the mean **functional scan. The structural images were then coregistered to the mean functional image and** parcellated into 90 cortical and subcortical regions of interest (ROIs) with the AAL atlas (Tzourio-Mazoyer et al., 2002), using a customized version of the IBASPM toolbox (Alemán-Gómez Y., 2006). **Each subject's structural atlas was obtained by warping the AAL atlas in the Montreal Neurological Institute (MNI) space onto the subject's space using the inverse transformation of the subject's structural image to MNI.** This structural atlas was then resampled **to the resolution of the functional images** to obtain a functional atlas. All the atlases were visually inspected in **each individual's** na**ti**ve space for quality control. The mean time series of each ROI was then extracted. To avoid potential confounds of slow drifts, due to magnetic susceptibility, the signal was linearly detrended**.** Furthermore, to account for the increased tendency of movement within the population under study, we also regressed the motion regressors as well as the average white matter signal from the time-series. This step was **equally** included in our previous paper (Scariati et al., 2014). An orthogonal cubic B-spline wavelet transform was used to filter the signal and keep the frequency range that had the highest signal to noise ratio for resting-state fluctuations (0.05-0.1Hz) (Achard et al., 2006). Finally, to provide a stronger control for motion compared to previous work (Scariati et al., 2014), the time-series were scrubbed based on the computation of the Framewise Displacement (FD) (Power et al., 2012). The volumes where FD was higher than 0.5, as well as the **preceding** and following volumes, were removed from the time-series. No**ne of the** subject**s** fulfilled usual criteria for excessive scrubbing (<5min final signal (Power et al., 2012)). Due to several participants exhibiting **signal drop** in the globus pallidus, this region was excluded bilaterally. Pairwise Pearson correlation coefficients between **each** regions' time courses were used as measures of functional connectivity. This resulted in a connectivity matrix of 88x88 regions with 3828 undirected weighted connections for each subject.

2.4. Brain connectivity analysis:

*2.4.1. **Graph thresholding**:*

The analysis of the functional connectomes was performed using the Brain Connectivity Toolbox (BCT, (Rubinov & Sporns, 2010)). The graphs were thresholded using a minimum spanning three algorithm followed by global thresholding (A. F. Alexander-Bloch et al., 2010; Hagmann et al., 2008). This method prevents the graphs from being divided in**to** several components after removal of the weakest connections. In order to understand the effect of thresholding, the analyses were performed on a range of graphs with different costs or densities (proportion of existing connections over the total number of possible connections) from an average degree of 3 until 35 by steps of 1. The lowest threshold (average degree of 2) was discarded as its mean clustering coefficient is 0 by definition. The maximal average degree of 35 was selected because it corresponded to a density of 40% for both groups. This led to the

computation of 33 graphs with increasing density for each subject. Notably no negative correlations were present in the graphs after thresholding.

2.4.2. Modularity coefficient computation:

The modularity coefficient quantifies the possibility to divide the network into groups of highly connected regions (modules) minimizing the number of connections between the groups (Blondel et al., 2008; Newman, 2006). It measures the segregation between the modules by computing the ratio between the intra- and intermodular connections (Newman, 2004). The modularity index was computed for each subject at each of the 33 density thresholds. Due to the non-convex nature of the modularity criterion, the algorithm was run 100 times with random initializations and the best solution was kept. For the statistical testing, age and gender effects were removed from the data using a linear regression prior to performing a Wilcoxon rank sum (WRS) test on the residuals. To test for the overall significance of the difference, we also measured the between-group difference in the area under the curve (AUC) for modularity. Finally, to ascertain that the graphs had a modular structure in both groups, we compared their modularity to the modularity of 1000 random graphs with preserved degree distribution and connectedness (Maslov & Sneppen, 2002), using a WRS test.

2.4.3. Modular organization:

The modules' decomposition was analyzed at the group level. The modularity algorithm was run 100 times on the group-averaged matrices at each density threshold, as previously described. The most stable community decomposition was identified as the partition that had the lowest distance (measured with the normalized variation of information (Meila, 2007)) to all the others. Statistical significance between the groups was tested using a permutation test with 499 surrogates. The **surrogate distance distribution** was obtained by randomly dividing the subjects into two groups and computing the distance between the most stable surrogate group-averaged modularity partitions. BrainNet Viewer ((Xia et al., 2013), http://www.nitrc.org/projects/bnv/) and TrackVis (http://trackvis.org) were used for the figures.

2.4.4. Local difference in modularity partition:

The local difference in modularity partition aims at quantitatively measuring the between-groups difference in module membership of each brain region. It was calculated as follows: 1) for each ROI, the regions that belonged to the same module were stored in a binary vector for both groups; 2) the distance between the two vectors was computed (1-Jaccard index) giving a measure of distance per ROI for each density threshold; 3) the statistical significance of the difference between the groups was tested via the same permutation test described in methods section *2.4.**3***. The results were corrected for multiple comparisons using maximum statistic (Nichols & Holmes, 2002).

We present in the Results section the AUC for this local measure because it shows which regions differ for module membership between patients and controls regardless of graph density. Thus it offers a summary measure of local differences in module membership. When the differences in modularity partition did not cover the entire range of densities tested, we computed the AUC for the

local differences only for the graph densities that showed a different modular organization. This aimed to identify which regions were driving the alterations we observed. We also performed the same analysis **to include** all the density thresholds but these results **were** mentioned only if they differ**ed from the ones presented in the "Results" section**. **Pairwise analyses of modules membership at each cost were also performed and show the variability of this measure as a factor of density. These results are presented in the Supplementary Material.**

2.4.5. Modularity analysis in age groups:

To reveal potential differences in the development of brain modules, we further subdivided our groups according to age: the subgroup of children and adolescents comprised participants aged from 9 to 17.9 years and the adult group was composed of participants aged between 18 and 30 years. Demographic information for all the groups can be found in Table 1. For both subgroups there were no significant differences in age, gender or movement parameters; IQ, however, was significantly lower in the patients' subgroups **compared to** the controls. Nine control participants younger than 18 and **five** control participants older than 18 had a sibling with the 22q11DS included in the study. The analyses after the removal of these subjects can be found in the Supplementary Material, but we mention the results that are different in the Results section. The modularity analysis was repeated in each subgroup as described above.

3. Results:

3.1. Modularity index:

The modularity index was significantly increased in patients compared to controls at all the density levels (Figure 1). The AUC was also significantly higher in 22q11DS (WRS test p=0.0081; median AUC for patients: 13.8; for controls: 12.5). However, for both groups, modularity was still higher than the modularity of randomized networks.

Using a Pearson correlation coefficient, we found no association within **either** group between modularity index AUC and age (control group: R=-0.01, p=0.9; 22q11DS group: R=0.03, p=0.8) or IQ (control group: R=0.03, p=0.87; 22q11DS group: R=0.09, p=0.54). When density thresholds were tested individually, the modularity index showed **no association with age or IQ in the control group.** In patients, the modularity index was correlated with IQ (for the lowest density graphs, <7%), but not with age (Supplementary Material, Figures S1 and S2).

Insert Figure 1 around here

3.2. Modular organization:

For both diagnostic groups, the number of modules decreased with increased network density as little modules merged together to form bigger ones, revealing **a** hierarchical organization that is shown in Figure 2. Overall, the

patients had one more module than the controls. With the exception of a few regions, notably the right inferior temporal gyrus, the modules were symmetric.

Modular organization was significantly different between the 22q11DS and the control groups over the whole range of costs tested except **for** three (31%, 37% and 38%) that showed strong trends in the same direction but did not reach significance (0.06>p>0.07). The most representative modular organization for each group (the one with the shortest distance to all other thresholds) is shown in Figure 3 (left column). Maps for all the thresholds can be seen in Video 1. In the control group, the modules corresponded globally to known functional networks, such as the DMN, the sensory-motor network, the auditory network (sometimes also including verbal regions), the visual network and the medial temporal network (Rosazza & Minati, 2011). In the 22q11DS group, the visual network was preserved, except for the absence of the inferior temporal gyrus. Furthermore, there was a lateral fronto-parietal module that was not seen **in** the control group and which included the sensory-motor regions, the dorsolateral prefrontal cortex (DLPFC) and the lateral parietal regions. The ROI**s** that showed **a** significant difference in module membership included all the brain regions except for occipital lobe areas (Figure 3 bottom). Maximal differences for this measure were located in the right inferior temporal gyrus, bilateral caudate nucleus, DLPFC, superior and inferior parietal lobules and orbitofrontal regions.

3.3. Modularity analysis in age subgroups:

In the comparison between patients and controls younger than 18, **the** modularity coefficient **in the graphs with costs between 7% and 20%** was significantly increased in the 22q11DS group compared to the young control group (WRS test for AUC: p=0.04, median AUC for controls: 12.2, for patients: 13.7). Differences in modular organization were seen only for the lowest density graphs (cost between 3% and 17%). When siblings **were** removed from the control group, the modularity coefficient **was** significantly different **for** a wider density range (2% to 29%) but the modularity partition **was** significantly different **for** a smaller density range (2% to 9%) (See Supplementary Material for complete results). The most representative modularity partitions for this age group are depicted in Figure 3 (middle column) and in the Supplementary Material Figure S10. Notably, the lateral fronto-parietal module was present in both groups.

To show which ROIs were driving the observed difference in modular communities, we included only the graph densities that were significantly different for modular organization (7%-20%) in the computation of the local differences in module membership. The strongest differences were located in the inferior temporal gyrus, anterior cingulate cortex (ACC), inferior parietal cortex and caudate nucleus bilaterally. All the results are shown in Figure 3 (bottom line). When the analysis was repeated **to include** all the density thresholds, several ROIs, including ACC, medial frontal, orbitofrontal and precuneus, remained significantly different **in terms of** module membership. However, the superior parietal gyrus lost significance while the superior frontal gyrus and the whole cingulate cortex became significant. Complete results are shown in **the** Supplementary Material (Figure S9).

In the adult subgroup comparison, the modularity coefficient was significantly increased in 22q11DS compared to controls for several graph densities (2%, 22%, 23% and 30% to 40%), but this result was not significant when the siblings **were** removed from the control group. The AUC only showed a trend significance (WRS test : p=0.075, median AUC for controls : 12.6, for patients : 14.1). Significant differences in modularity partition were observed at all thresholds in the adult comparison. The lateral fronto-parietal module was only observed in adults with 22q11DS, but was absent in the adult control group (Figure 3 right column). As in the whole group analysis, all the ROIs except the occipital regions showed a significant difference in module membership. Supplementary Figure 1 B summarizes the hierarchical organization and the most stable modularity partitions for both groups.

When the healthy controls that had a sibling in the patients' group were removed, the local difference in modularity partition did not reach significance for any ROI for both age subgroups. **Since** the modular organization showed closely related results and the average modularity partition was only marginally modified when the siblings were removed, **any** difference is likely due to the reduced sample size.

Insert Figure 2 around here

4. Discussion

To the best of our knowledge, this is the first study to analyze modularity decomposition of the functional brain network in patients with 22q11DS. We provide evidence for increased segregation between modules and altered modularity partition **in** 22q11DS, mainly located in the superior parietal, frontal and inferior temporal lobes. The analysis performed in age subgroups reveals that visual, parietal and medial frontal alterations are present in children and adolescents as well as in adults with 22q11DS. By contrast altered module membership of the DLPFC is characteristic of the adult patients. These results show the presence of abnormal functional connectivity in networks sustaining impaired cognitive functions in 22q11DS, such as the visuo-spatial network. They also suggest an altered development of frontal brain connectivity in the microdeletion.

4.1. Segregation between modules is increased in 22q11DS

We observe an increased modularity in the 22q11DS group, which indicates decreased connectivity between the modules, and increased network segregation. This is in line with previous results showing an increased brain network segregation in 22q11DS using DTI (Ottet et al., 2013). A similar increase in modularity has also been previously described in autism (Barttfeld et al., 2011), Parkinson**'s** disease (Baggio et al., 2014) and in children with frontal lobe epilepsy (Vaessen et al., 2013)**,** and was associated with poorer cognitive capacities in the latter two studies. Conversely, one study found a positive association between working memory and modularity (Stevens et al., 2012), and described a decrease in modularity in childhood onset schizophrenia (A. Alexander-Bloch et al., 2013; A. F. Alexander-Bloch et al., 2010). Findings from these studies suggest that modularity is related to cognitive capacities, possibly

by decreasing the ability of the network to integrate different modalities of information into a coherent picture. However, we identify an association between modularity and IQ in 22q11DS **for** only a few **of the** graph densities. In our opinion, the absence of an association between these two global measures does not exclude the possible participation of network segregation in cognitive deficits. Local measures, however, may be more representative of specific cognitive deficits and such associations may be identified with hypothesis driven studies targeting specific resting-state networks.

4.2. Reorganization of modular communities in patients with 22q11DS:

Studies performed in healthy populations consistently show the existence of three major modules: a posterior visual module, a central module and an anterior module (Fair et al., 2009; He et al., 2009; Meunier et al., 2009; Meunier et al., 2010). The most stable community partition identified in our control group closely corresponds to this description except that the medial temporal structures are further separated in a fourth module (Figure 2 left column). Moreover, consistent with previous studies, our results are strongly symmetric (Chen et al., 2008; Schwarz et al., 2008) and hierarchical (Gallos et al., 2012; Meunier et al., 2010). Indeed, when weaker connections are removed, the modules are split into smaller units that correspond more closely to brain functions (Figure 3 and Video 1). In patients with 22q11DS, we identify alterations of modular communities that particularly affect the visuo-spatial regions, the ACC and the lateral prefrontal regions.

Insert Figure 3 around here

Visuo-spatial brain regions, notably the bilateral superior parietal and the right inferior temporal gyri, are clustered with primary visual regions in control participants but not in patients with 22q11DS. These regions are respectively part of the "where" dorsal pathway, responsible for object spatial localization (Creem & Proffitt, 2001), and the "what" ventral stream that sustains object and face recognition (Creem & Proffitt, 2001). Both pathways are thought to be impaired in patients with the microdeletion as deficits in visuo-spatial skills (Antshel et al., 2008), face recognition (Andersson et al., 2008; Lajiness-O'Neill et al., 2005) and social skills (K. Baker & Vorstman, 2012; K. D. Baker & Skuse, 2005) have been consistently described in 22q11DS**.** Furthermore, functional connectivity alterations of high-level visual networks had already been identified in our former ICA study (Debbane et al., 2012), and abnormal white matter structure in parietal regions **have** been described in DTI studies including both with increased (da Silva Alves et al., 2011; Simon et al., 2005; Simon et al., 2008) and decreased (Barnea-Goraly et al., 2005; Barnea-Goraly et al., 2003; Sundram et al., 2010) fractional anisotropy. Here, we provide further evidence for early functional dysconnectivity of visual processing pathways in 22q11DS using a larger sample size and a different methodology.

The ACC is another region that shows a strong difference of community partition across all age groups. Alterations of the ACC have been consistently identified in 22q11DS with structural (Dufour et al., 2008; Jalbrzikowski et al., 2013; Schaer et al., 2010) and functional MRI (Scariati et al., 2014; Schneider et al., 2012) as well as with electroencephalography (EEG) (Rihs et al., 2012;

Tomescu et al., 2014). In our results, the ACC is associated with DMN regions at almost all density thresholds in patients. However, in the healthy controls, the ACC is subsequently included in the same module as orbitofrontal, DMN and DLPFC regions (Supplementary Figure 1A). In studies performed on healthy populations, **the** ACC has shown connections with all three networks: the DMN (Raichle et al., 2001; Rosazza & Minati, 2011) for its involvement in the sense of self (Murray et al., 2012), the DLPFC for a possible contribution to executive functions (Cohen et al., 2005; Gasquoine, 2013) and the orbitofrontal cortex for reward estimation, learning and conflict monitoring (Botvinick, 2007; Cohen et al., 2005). Our results suggest a decreased participation of the ACC in these different networks in 22q11DS. Altered dynamic connectivity of the ACC was also suggested by two recent EEG studies (Tomescu et al., 2014; Tomescu et al., 2015) that showed an increased presence of microstate C**,** which has been shown to correlate positively with fMRI recorded activity in the ACC (Britz et al., 2010). Recently developed techniques for analyzing dynamic resting-state connectivity with fMRI (Leonardi et al., 2013; Zalesky et al., 2014) may be used to confirm this hypothesis.

Through its participation in self-monitoring and saliency, the ACC has shown to be associated with psychotic symptoms in 22q11DS (Dufour et al., 2008; Scariati et al., 2014; Schneider et al., 2012; Tomescu et al., 2014) and in the general population (Allen et al., 2008; Menon, 2011). Notably, in our previous fMRI study, we showed that this region played an important role in identifying the patients **suffering from prodromal psychotic symptoms within a population of patients with 22q11DS** (Scariati et al., 2014). The current results show that ACC functional connectivity alterations are already present in our sample of children and adolescents with the microdeletion, providing further support for considering the ACC as a potential biomarker for an increased psychosis risk. Ongoing longitudinal studies will be necessary to confirm the predictive value of ACC for psychosis development.

In addition to the alterations discussed above, the altered modular membership of the DLPFC is only present in adults. During childhood and adolescence both patients and control participants show a fronto-parietal module that includes the DLPFC, sensory-motor and superior parietal regions. This network is also observed in adults with the microdeletion but absent in adult controls, where it is divided into several modules that all have a stronger correspondence with functional networks (Figure 3). The difference we observe between younger and older control subgroups is consistent with previous literature showing that resting-state networks evolve with age from a preferentially local pattern of connectivity to a more distant and functionally defined community structure (Dosenbach et al., 2010; Fair et al., 2008; Fair et al., 2009). However, in 22q11DS, the presence of the fronto-parietal module in adults suggests an altered development of frontal connectivity with age. Previous structural neuroimaging studies have shown that frontal lobe volume is preserved in children and decreased in adults with the microdeletion (Gothelf et al., 2008), which suggests an excessive pruning of frontal lobe connections during adolescence (Schaer et al., 2009). The presence of abnormal pruning is also supported by DTI studies showing that white matter abnormalities in 22q11DS are likely related to axonal damage (Jalbrzikowski et al., 2014; Kikinis

et al., 2012). However, according to computational models, pruning plays a role in shaping modular communities (Stam et al., 2010; Vertes et al., 2012) by favoring connections between distant but functionally related regions (Fair et al., 2008; Fair et al., 2007). Again, longitudinal studies will be needed to confirm the presence of altered trajectories of functional connectivity development in 22q11DS.

There are a number of limitations to this study. Firstly, despite the 22q11DS being a recognized genetic model for schizophrenia, patients also present a reduced IQ and comorbid psychiatric diseases (Schneider, Debbane, et al., 2014). Thus, ACC dysconnectivity may also contribute to the cognitive difficulties observed in 22q11DS (Antshel et al., 2008). However, as cognitive deficits are also found in patients with schizophrenia, it may not be possible to disentangle the two phenomena **as they** could share common mechanisms. We decided not to use IQ as a covariate since low IQ is directly associated to diagnosis. Only the addition of a control group matched for IQ could accurately remove this effect (Miller & Chapman, 2001). Comorbid psychiatric disorders and **the use of** psychotropic medication were also present only in the 22q11DS group and are potential confounding factors. Secondly, the population with 22q11DS has an increased **tendence for** motion during MRI acquisition**s**. Even if we used state of the art techniques for motion correction, a residual effect of movement may still remain. Nevertheless, decreased modularity has been associated to motion (as demonstrated by (Satterthwaite et al., 2012)) while we observed an increase. Finally, the fact that we use a group averaged matrix to compute the modules prevent**ed** us from looking at age as a continuous variable and constrain**ed** us to make a categorical division of age. Longitudinal studies are warranted to refine the developmental curves of brain connectivity in 22q11DS.

5. Conclusion:

To our knowledge, this study is the first to investigate whole-brain communities of functional networks in 22q11DS across age groups. We identify altered community partitioning of the visuo-spatial network and ACC that are already present in children and adolescents. Given the strong association between ACC alterations and psychosis in individuals with the 22q11DS, these results provide further evidence for considering ACC as a potential early biomarker for schizophrenia **and** should **thus** be tested in future longitudinal studies. Furthermore, the presence of DLPFC modularity alterations in only the adults suggests an altered development of prefrontal community structure during adolescence in 22q11DS.

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Notes:

The authors declare no conflict of interest

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Captions

Figure 1: Plots of modularity coefficient (top) and p values of modularity coefficient (middle) and modular organization (bottom) for the comparison between the patients with 22q11DS and healthy controls. Results for the whole sample are shown on the left, for the children and adolescents in the middle and for the adults on the right. All these values are plotted against graph density. For the top **row**, the modularity coefficient is shown with red dots for the patients, and with blue triangles for healthy controls. **Mean modularity coefficients for the random graphs** are shown in dashed lines in red for patients and blue for healthy controls. For the two bottom rows, significance (p=0.05) is indicated by a green dashed line, a red dashed line indicates p=0.1.

Figure 2: Modularity partition over different graph density thresholds
The number of modules is plotted against graph density with blue triangles for controls and red dots for patients with 22q11DS. The modularity partition is displayed for both groups (patients over the curve and controls below) for densities with 7, 5 and 4 modules. The modularity partition **that was selected** to display **was** the one that had the **shorter** distance to all other partition**s** with the same number of modules for each group. All the modularity partitions and the subcortical structures can be seen in Video 1.

Figure 3: Average modularity partition for patients with 22q11DS and healthy controls in the whole sample, the child/adolescent group and the adult group
The modularity partitions of the control group (1st **row**) and of the 22q11DS group (2nd **row**) are shown for the most stable community partition (i.e. **the** partition that has the **shortest** distance to the community partitions of all the other density thresholds). The 1st column corresponds to the analysis performed on the whole sample, the 2nd column to the analysis performed on the subgroup of children and adolescents and the 3rd column to the analysis performed on the subgroup of adults. The last **row** shows the regional difference in community partition between the two groups summed over the thresholds that are significantly different between the groups for modular organization. Each cell corresponds to the difference between the two cells above. Only regions with significant differences ($p<0.05$ corrected for maximum statistic) are shown (the lighter the color, the bigger the difference), non-significant regions are in gray.

Video 1: Modularity partition over the graph densities for patients with 22q11.2 deletion syndrome and healthy participants:
Brain maps of the modularity partitions are shown on the left for healthy controls and on the right for patients with the 22q11.2 deletion syndrome. The graph density as well as the corresponding average connectivity matrix for each group are shown below.

Table 1: Demographic information

	All			Children and adolescents			Adults		
	HC	**22q11DS**	**p value**	**HC**	**22q11DS**	**p value**	**HC**	**22q11DS**	**p value**
Gender N(M/F)	41(20/21)	40(21/19)	0.74	24(11/13)	25(12/13)	0.75	17(9/8)	15(8/7)	0.853
Age	18+/-5	17+/-5	0.51	13.9+/-2	13.8+/-2	0.72	23.2+/-4	22.1+/-3	0.575
dQ	109+/-16	67+/-12	**<0.0001***	112+/-15	69+/-13	**<0.0001***	104+/-15	61+/-6	**<0.0001***
Laterality	33R, 4L, 4B	35R, 3L, 2B	0.65	16R, 4L, 4B	20R, 3L, 2B	0.74	17R	15R	-
ADHD	-	11	-	-	11	-	-	0	-
Any Mood disorder	-	5	-	-	3	-	-	2	-
Any anxiety disorder	-	11	-	-	6	-	-	5	-
Other psychiatric disorders	-	4	-	-	4	-	-	0	-
Any psychotic disorder	-	4	-	-	2	-	-	2	-
≥1 psychotropic medication	-	14	-	-	7	-	-	7	-
Medication	-	Methylphenidate: 6; Anxiolytics: 2; Antidepressants 3; Melatonine: 5; Neuroleptics: 5; Antiepileptics: 3	-	-	Methylphenidate:4; Anxiolytics: 1; Antidepressants 1; Melatonine: 4; Neuroleptics: 2; Antiepileptics: 1	-	-	Methylphenidate:2; Anxiolytics: 1; Antidepressants 2; Melatonine: 1; Neuroleptics: 3; Antiepileptics: 2	-

Between-group differences were tested with a two sample T-test for the continuous variables and a Chi-square test for the discrete variables. For laterality R=right handed, L= left handed and B=ambidextrous. The "Other psychiatric disorders" category includes oppositional disorders as well as enuresia and encopresia. "*" and bold font indicates statistically significant differences between the groups.

Figure 1

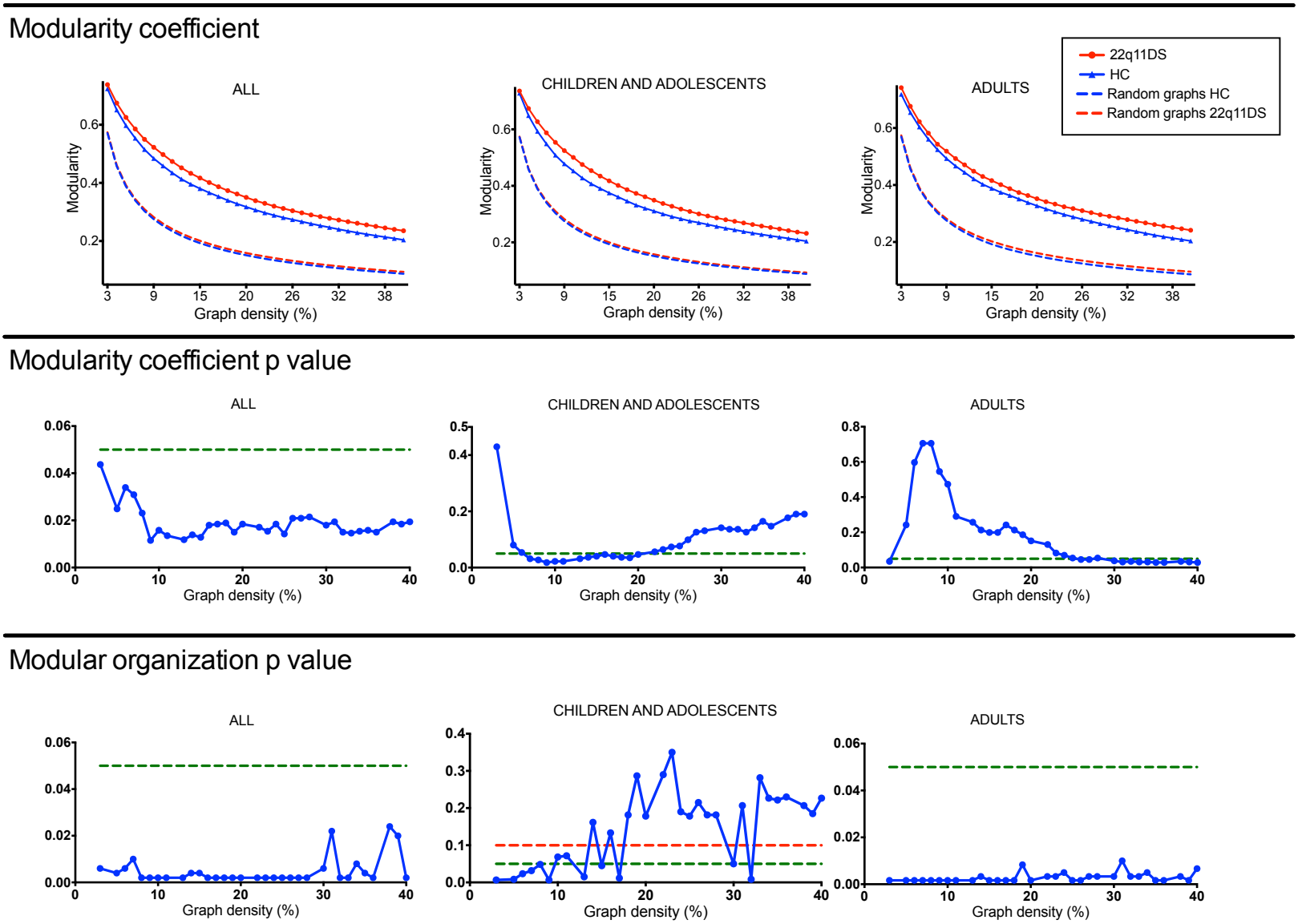

Modularity coefficient
ALL
CHILDREN AND ADOLESCENTS
ADULTS
22q11DS
HC
Random graphs HC
Random graphs 22q11DS
Modularity
Graph density (%)
Modularity coefficient p value
Modular organization p value

Figure 2

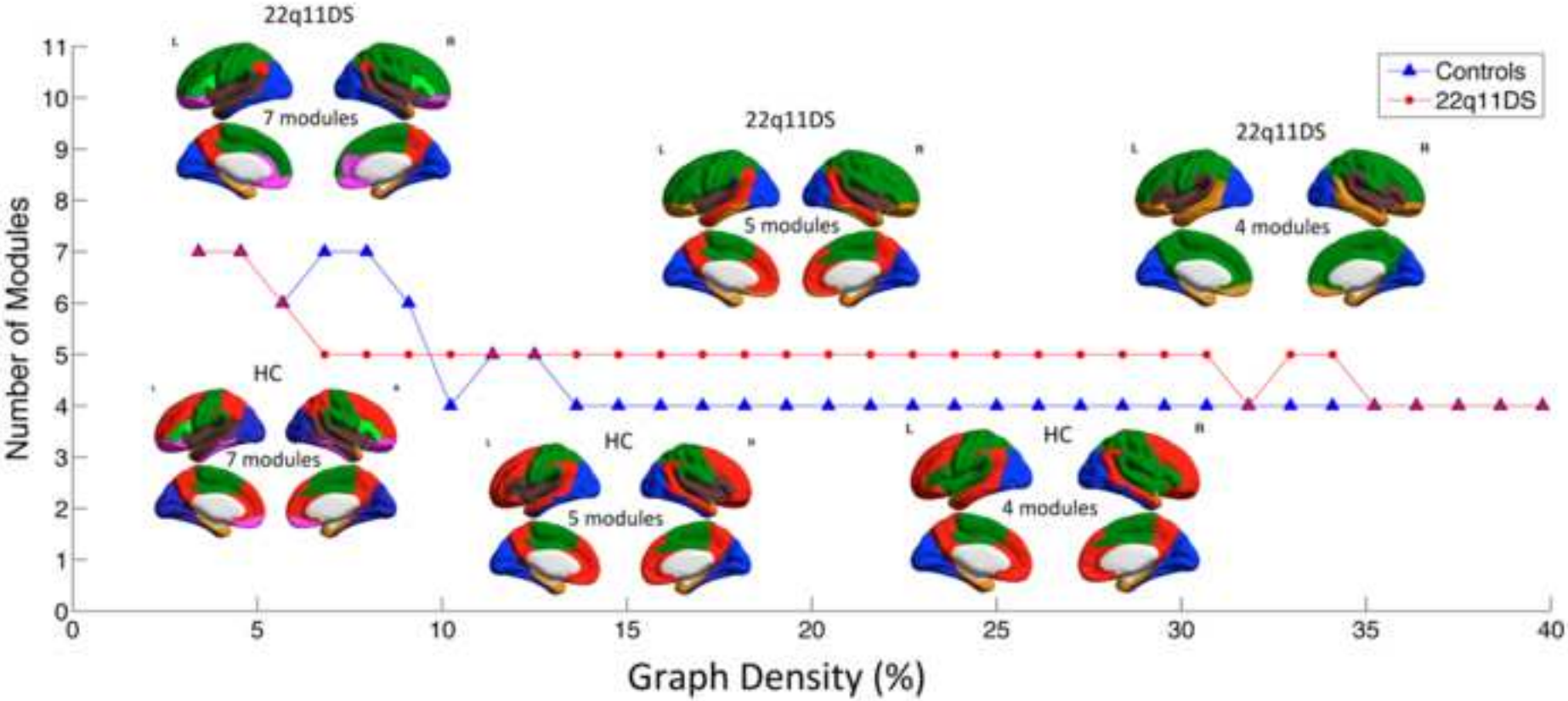
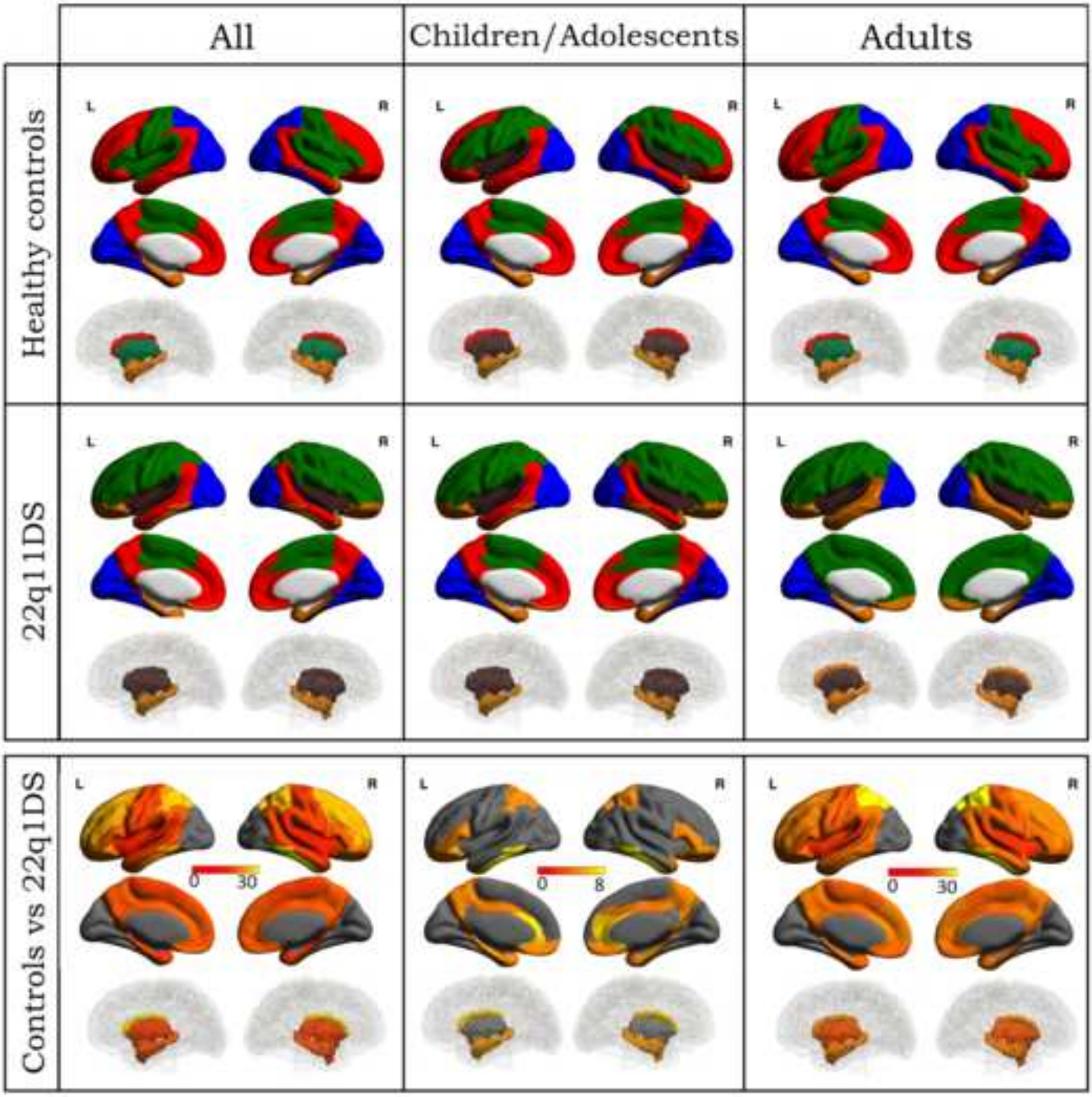

22q11DS
7 modules
22q11DS
5 modules
22q11DS
4 modules
HC
7 modules
HC
5 modules
HC
4 modules
Controls
22q11DS
Number of Modules
Graph Density (%)
0
1
2
3
4
5
6
7
8
9
10
11
0
5
10
15
20
25
30
35
40

Figure 3


All
Children/Adolescents
Adults
Healthy controls
22q11DS
Controls vs 22q1DS
L
R
0
30
0
8
0
30