Title

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Journal

Social Cognitive and Affective Neuroscience, 9(9)

ISSN

1749-5016

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Publication Date

2014-09-01

DOI

10.1093/scan/nst114

Peer reviewed

doi:10.1093/scan/nst114 SCAN (2014) 9, 1261–1267

Default mode network connectivity and reciprocal social behavior in 22q11.2 deletion syndrome

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22q11.2 deletion syndrome (22q11DS) is a genetic mutation associated with disorders of cortical connectivity and social dysfunction. However, little is known about the functional connectivity (FC) of the resting brain in 22q11DS and its relationship with social behavior. A seed-based analysis of resting-state functional magnetic resonance imaging data was used to investigate FC associated with the posterior cingulate cortex (PCC), in (26) youth with 22qDS and (51) demographically matched controls. Subsequently, the relationship between PCC connectivity and Social Responsiveness Scale (SRS) scores was examined in 22q11DS participants. Relative to 22q11DS participants, controls showed significantly stronger FC between the PCC and other default mode network (DMN) nodes, including the precuneus, precentral gyrus and left frontal pole. 22q11DS patients did not show age-associated FC changes observed in typically developing controls. Increased connectivity between PCC, medial prefrontal regions and the anterior cingulate cortex, was associated with lower SRS scores (i.e. improved social competence) in 22q11DS. DMN integrity may play a key role in social information processing. We observed disrupted DMN connectivity in 22q11DS, paralleling reports from idiopathic autism and schizophrenia. Increased strength of long-range DMN connectivity was associated with improved social functioning in 22q11DS. These findings support a 'developmental-disconnection' hypothesis of symptom development in this disorder.

Keywords: functional MRI; resting state; velocardiofacial syndrome; dysconnectivity

INTRODUCTION

Neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia are increasingly conceptualized as disorders of cortical connectivity, and current evidence suggests that both of these conditions involve inappropriate circuit formation due to aberrant neurodevelopment (Insel, 2010; Meechan *et al.*, 2012). 22q11.2 deletion syndrome (velocardiofacial/DiGeorge syndrome; 22q11DS) is a genetic disorder that represents one of the most significant genetic risk factors known for the development of these 'connectopathies' (Karayiorgou *et al.*, 2010). This microdeletion afflicts about 1 in 4000 live births, and is estimated to account for 1–2% of schizophrenia cases, representing the only known recurrent copy number mutation responsible for introducing new cases of schizophrenia into the population (Karayiorgou *et al.*, 2010). Furthermore, the prevalence of ASD in children with 22q11DS ranges from 24% to 50%, indicating that disorders associated with social behavioral dysfunction are a highly penetrant aspect of the 22q11DS phenotype. The deletion encompasses between 1.5 and 3 Mb, encoding 30–60 known genes. Phenotypic consequences of the deletion are variable, ranging from cardiac defects and immunodeficiency to language delays and cognitive impairment (Drew *et al.*, 2011). At present, the genetic and neurobiological mechanisms accounting for elevated psychiatric risk in 22q11DS have yet to be fully elucidated. Despite existing evidence for social and neurocognitive dysfunction in 22q11DS (Jalbrzikowski *et al.*, 2012) and the plausibility of aberrant intrinsic brain connectivity as an integral factor in these aspects of the phenotype, direct assays of the impact of the deletion on brain function in humans have only recently been initiated (Gothelf *et al.*, 2007; Debbané *et al.*, 2012).

Since the first reports of synchronized functional correlations in low frequency blood oxygen level dependent (BOLD) signal within the motor system at rest (Biswal *et al.*, 1997), interest in the potential of resting-state functional magnetic resonance imaging (rs-fMRI) to characterize the brain's intrinsic functional architecture has grown exponentially. Functional connectivity (FC) mapping approaches have led to the discovery of several putative resting state networks (RSNs), which have been shown to be robust and reproducible across participants and time (Damoiseaux *et al.,* 2006; De Luca *et al.,* 2006; Kalcher *et al.,* 2012). The best characterized of these is the default mode network (DMN), a collection of spatially distinct regions spanning the medial prefrontal, lateral parietal and posterior cingulate cortices (PCCs), that is more active in the absence of an overt cognitive task and is implicated in social cognition, mind wandering and self-referential thought (Raichle *et al.*, 2001; Greicius *et al.*, 2003; Rosazza *et al.*, 2011). Aberrant connectivity within the DMN has been implicated in a number of neuropsychiatric disorders, and accordingly, the dynamics of this RSN and the degree of network dysfunction may serve as a valuable biomarker for nascent psychiatric disorders in at-risk individuals (Broyd *et al.*, 2009; Soddu *et al.*, 2011; Whitfield-Gabrieli and Ford, 2012). As such, mapping the functional architecture of the brain in 22q11DS may help to elucidate gene–brain–behavior relationships. We hypothesized that individuals with 22q11DS would show reduced intra-network FC between the major hub regions of the DMN, the PCC and ventromedial prefrontal cortex (Uddin *et al.*, 2009), in accordance with existing evidence for DMN dysfunction in both idiopathic schizophrenia and ASD (Broyd *et al.*, 2009; Assaf *et al.*,

Received 2 April 2013; Revised 3 June 2013; Accepted 17 July 2013
Advance Access publication 2 August 2013

This study was performed at the Semel Institute for Neuroscience and Human Behavior (Department of Psychiatry & Biobehavioral Sciences, UCLA) and was presented in part at the Annual Meeting of the Society for Biological Psychiatry, 16–18 May 2013, San Francisco, CA, USA.

This study was supported by grants from the National Institute of Mental Health (RO1 MH085953 to C.E.B.); NIH/NICHD (grant P50-HD-055784 Pilot Project Grant to C.E.B.); Neuroimaging Training Program Fellowship (T32 T90DA022768 to M.J.S.), UL1 Coordinating Center Grant (UL1-DE019580 and PL1MH083271 to R.B.) and K01MH092288 (to L.Q.U.).

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2010; Rudie *et al.*, 2012). Secondly, given known developmental shifts in patterns of functional brain connectivity (Uddin *et al.*, 2010), we investigated age effects on DMN connectivity, with the hypothesis that 22q11DS patients would fail to show the typical developmental pattern of 'local to distributed' organization with increasing age (Fair *et al.*, 2009). Finally, as social impairment is a fundamental aspect of both idiopathic schizophrenia and ASD, we investigated whether abnormalities in DMN connectivity were associated with impairment in reciprocal social behavior in 22q11DS. Given the DMN's critical role in social information processing, we hypothesized that increased connectivity within DMN regions would be associated with better social competence.

MATERIALS AND METHODS

Participants

The total (initial) sample consisting of 87 participants aged 6–28 years (31 patients with a molecularly confirmed diagnosis of a 22q11.2 microdeletion and 56 age- and sex-matched typically developing controls) was recruited from an ongoing longitudinal study at the University of California, Los Angeles. Exclusion criteria for all study participants were: additional neurological or medical condition that might affect imaging measures, insufficient fluency in English, endorsement of substance or alcohol abuse and/or dependence within the past 6 months and any condition that is a contraindication for MRI (pregnancy, claustrophobia, etc.). Healthy controls additionally did not meet criteria for any major mental disorder, based on information gathered during administration of the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID; (First *et al.*, 1996)], with an additional developmental disorders module, as applied by Addington *et al.* (2012) (for participants over the age of 16 years) and/or the Computerized Diagnostic Interview Schedule for Children [C-DISC; (Jensen *et al.*, 1995)] for participants aged $\leq$16 years. Diagnoses of autism spectrum disorder were determined using the Autism Diagnostic Observation Schedule (Lord *et al.*, 2000) administered to the child and the Autism Diagnostic Interview-Revised (Lord *et al.*, 1994), administered to the subject's parent/primary caretaker. All clinical interviews were conducted by highly trained MA- or PhD-level psychologists; inter-rater reliability and case consensus procedures have been described in detail elsewhere (Meyer *et al.*, 2005; Ho *et al.*, 2012). All participants and/or their parents underwent a verbal and written informed consent process after complete description of the study. The UCLA Institutional Review Board approved all study protocols. Table 1 provides demographic information for all participants included in our [group-level fMRI] analyses, [following exclusion of subjects with excess motion (see below) during their scan].

Table 1 Subject Demographics[a]

	22q11DS participants ($N = 26$)	Typically developing controls ($N = 51$)	*P*-value
Age [mean $\pm$ s.d.(range)]	15.9 $\pm$ 4.9 (8–26)	14.4 $\pm$ 6.4 (6–28)	0.273
Gender, male; *n* (%)	17 (65)	28 (55)	0.384
Full Scale IQ (mean $\pm$ s.d.)	78.6 $\pm$ 15.8	114.1 $\pm$ 20.8	<0.0001
SRS *t*–score[b] (mean $\pm$ s.d.)	70.8 $\pm$ 16.7	47.5 $\pm$ 10.4	<0.0001
Autism spectrum disorder diagnosis, *n* (%)	10 (38)	0 (0)	<0.0001
Psychotic disorder diagnosis, *n* (%)	2 (8)	0 (0)	0.0454
ADHD diagnosis, *n* (%)	14 (54)	0 (0)	<0.0001]
ODD diagnosis, *n* (%)	1 (4)	0 (0)	0.1628]
Anxiety disorder diagnosis, *n* (%)	7 (27)	0 (0)	<0.0001]
Mood disorder diagnosis, *n* (%)	5 (19)	0 (0)	0.001]
Current antipsychotic treatment, *n* (%)	3 (12)	0 (0)	0.013
Current antidepressant treatment, *n* (%)	8 (31)	2 (4)	0.0007
Current psychostimulant treatment, *n* (%)	2 (8)	0 (0)	0.0454]
Scanner Site[c]	16 (62) BMC, 10 (38) CCN	31 (61) BMC, 20 (39) CCN	0.9497

[a]Five 22q11DS patients and five controls were excluded (from initial sample) due to excessive motion; [b]SRS data were not available for 16 controls; [c]no significant difference between distribution of medicated subjects between the two scanner sites.
ADHD, attention deficit hyperactivity disorder
ODD, oppositional defiant disorder

Neurobehavioral measures

Estimates of general intellectual functioning were obtained for all participants from the two-subtest (vocabulary and matrix reasoning) version of the Wechsler Abbreviated Scale of Intelligence (Lord *et al.*, 1994). Parents of study participants completed the Social Responsiveness Scale [SRS; (Meyer *et al.*, 2005)], a quantitative measure of reciprocal social behavior that has been extensively validated in both clinically ascertained and population-based samples. The measure represents the three criterion domains for autism and correlates strongly with a gold standard diagnosis of ASD based on the Autism Diagnostic Interview (Constantino *et al.*, 2003).

fMRI data acquisition

Structural and functional scans were acquired at either the Ahmanson–Lovelace Brain Mapping Center (BMC) or the Staglin Center for Cognitive Neuroscience (CCN) in Los Angeles, CA, USA. Both sites had an identical three Tesla Siemens Tim Trio system, utilizing a 12 channel head coil. The primary structural scan used for registration purposes consisted of a matched-bandwidth high-resolution T1 image [voxel size $1.5 \times 1.5 \times 4.0$ mm, echo time (TE) = 34 ms, repetition time (TR) = 5000 ms, echo spacing = 0.89 ms, 34 axial slices, slice thickness 4.0 mm, slice spacing 0 mm, flip angle 90°, field of view (FOV) = 210, matrix size = 128×128]. Subsequently, a 5 min resting state functional scan was acquired, during which a black screen was presented and participants were instructed to keep their eyes open, remain relaxed and attempt to avoid falling asleep. The resting state scan consisted of 152 BOLD 3D images (voxel size $3.0 \times 3.0 \times 4.0$ mm, TE = 30 ms, TR = 2000 ms, echo spacing = 0.79 ms, 34 axial slices, slice thickness 4.0 mm, slice spacing 0 mm, flip angle 90°, FOV = 192, matrix size = 64×64).

fMRI data pre-processing

All data were pre-processed and analyzed with tools from the FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/). Scans were obtained with an interleaved slice acquisition sequence, and no slice-timing-correction was applied. Each subject's full functional scan was motion-corrected by registering each image to the middle volume as a reference, using FMRIB's linear image registration tool. Any subject with >2 mm of translational motion or 2° of rotational motion was excluded from further analysis (controls = 5; 22q11DS = 5), resulting in 51 controls and 26 22q11DS patients with useable data. For the remaining subjects, there were no significant differences in rotational or translational motion between the two groups ($P = 0.6921$). The 4D functional images were skull stripped using FSL's Brain Extraction Tool and spatially smoothed with a 5 mm full width half maximum isotropic Gaussian kernel and bandpass temporal filtering ($0.005\,\text{Hz} < f < 0.1\,\text{Hz}$). An initial first level analysis was run in FMRI Expert Analysis Tool (FEAT), modeling the global signal and the six motion parameters, and the data were registered to the matched-bandwidth high-resolution T1 and then to Montreal Neurological Institute (MNI-152) space. Next, the residuals from this analysis were normalized to prepare for extraction of the timeseries, using the formula (residual-mean)/s.d.) to result in a mean of 0 and standard deviation

of 1. Then, a brain mask was created by adding 100 to each voxel and binarizing the image. A 6 mm region of interest (ROI) was placed in the posterior cingulate (PCC: MNI coordinates: 0, −52, 30; Supplementary Figure S1), following previously published work (De Luca *et al.*, 2006; Uddin *et al.*, 2009). These ROIs were registered to each subject's functional dataset (utilizing the transformation matrix derived from the earlier subject-to-standard space registration) and the mean time-series within the registered ROI was extracted from the original residuals file. For the primary connectivity analysis, the average time course of the PCC-seed was normalized and was entered into FEAT as an explanatory variable for the scaled residuals generated following pre-processing. Finally, the statistical contrast output from FEAT for each subject was normalized via Fisher's *z*-transformation and used as an input to the group-level analyses (described below). Additionally, we used statistical maps generated from the PCC ROI and extracted an index of the correlation of the PCC with the ventromedial prefrontal cortex (vmPFC; 6 mm diameter sphere centered at MNI coordinates: 4, 56, −12) to obtain a metric of PCC–vmPFC connectivity at rest and quantify the degree of correlation within the DMN between these two hub regions.

Group-level analyses

In order to rule out potential scanner-related differences, we checked for differences between scanners in each group, then for interactions between scanner and any covariates of interest in each group, for our two group-level analyses. Once it was determined that there were no differences between scanners, nor were there significant interactions between scanner and our model parameters, in any ROI (all $P > 0.05$), all subsequent group-level analyses were conducted with scanner location included in the model as a covariate. In order to investigate group-level effects on DMN connectivity, outputs from the participant-level analysis for each subject were entered into an ordinary least squares analysis. First, a between-groups comparison was conducted to investigate differences in whole-brain PCC-derived functional connectivity between 22q11DS patients *vs* controls (controlling for age, gender and scanner location); secondly, an interaction term (age × diagnosis) was added to the group comparison model, in order to explore differential effects of age on DMN connectivity between the two groups. Two-tailed *t*-tests were used to compare the strength of the *z*-transformed Pearson's correlation between the PCC seed and vmPFC seed between groups. Finally, a regression analysis within the 22q11DS group was conducted to investigate the association between SRS *t*-scores and PCC-derived FC (controlling for age, gender and scanner location). In all analyses, covariates (age, gender and SRS *t*-score) were demeaned. Cluster correction for multiple comparisons was carried out using Gaussian random field theory (min $z > 2.3$; cluster significance: $P < 0.05$, corrected).

RESULTS

Group differences in PCC connectivity

In both healthy controls and 22q11DS participants, regions in which spontaneous BOLD fluctuations were significantly correlated with the PCC include the precuneus, the vmPFC and portions of inferior/lateral parietal cortex; areas classically considered part of the DMN (Figure 1a). However, group comparisons revealed significant differences in both the spatial extent and magnitude of DMN connectivity. Controls showed significantly stronger FC between the PCC and other DMN regions, including the precuneus, the left and right precentral gyrus, the left frontal pole and left lateral occipito-parietal regions (Figure 1b). In contrast, 22q11DS participants displayed a more diffuse pattern of FC with the PCC (Figure 1b), involving significantly stronger connectivity with the right inferior frontal gyrus (IFG).

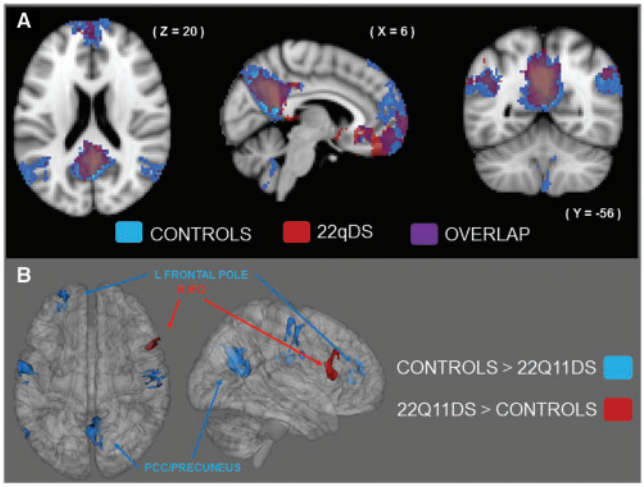

Fig. 1 PCC functional connectivity in 22q11DS patients and healthy controls. Top panel (1 a) depicts within-group functional connectivity. Red colors indicate regions of significant functional connectivity to the PCC in patients with 22q11DS, while blue colors indicate regions of significant functional connectivity to the PCC in healthy controls and purple indicates areas of overlap across groups. As seen here, both healthy controls and 22q11DS patients exhibit functional connectivity to areas classically considered part of the DMN, though the strength of the DMN network in 22q11DS patients, especially along long-distance connections, appears less robust. The bottom panel (1 b) depicts significant group differences in PCC connectivity between 22q11DS patients *vs* controls. As depicted here, controls showed significantly stronger functional connectivity between the PCC and other DMN regions, including the precuneus, the left and right precentral gyrus, the left frontal pole and left lateral occipito-parietal regions. In contrast, 22q11DS patients displayed a more diffuse pattern of functional connectivity with the PCC, involving significantly stronger correlations between the PCC and right inferior frontal gyrus.

Information on all cluster locations, sizes and significance can be found in Table 2.

Functional connectivity between DMN hubs

The strength of correlation between seed regions in the PCC and vmPFC was significantly greater for controls than for 22q11DS participants ($P = 0.0358$), providing further evidence of diminished within-network connectivity in 22q11DS (Supplementary Figure S2).

Age effects

22q11DS participants showed a distinct pattern of age-associated changes in FC with the PCC, relative to controls (Figure 2a). Group contrasts show that compared to 22q11DS participants, controls exhibited significantly increased connectivity between the PCC seed and right middle temporo-occipital cortex with increasing age, relative to 22q11DS participants (Table 2; Figure 2b). In contrast, 22q11DS participants show differential connectivity between the PCC seed, the right temporal pole/parahippocampal gyrus and inferior portions of the right lateral frontal cortex, with increasing age (Table 2; Figure 2b).

Association with social behavior in 22q11DS

Cortical areas with significant connectivity to the PCC that were also significantly associated with lower SRS scores (i.e. better social competence) were predominantly constrained to the right frontal cortex, including lateral and medial regions as well as portions of the anterior cingulate cortex (ACC) and paracingulate gyrus and left medial frontal pole (Table 2; Figure 3).

Medication effects

In order to account for any potentially confounding influence of psychotropic medications on our findings, the analyses described

Table 2 Significant Cluster Locations from Group Analyses

Contrast	Cluster index	Cluster size (voxels)	X	Y	Z	*P*-value	Anatomical region
CONT > 22qDS (Figure 1b)	1	432	6	−48	16	2.56E-06	Precuneus
	2	349	44	−12	48	3.22E-05	Right precentral gyrus
	3	284	−58	−6	28	2.69E-04	Left precentral gyrus
	4	227	−22	48	6	0.00198	Left frontal pole
	5	167	−54	−64	20	0.0195	Left lateral occipitoparietal regions
22qDS > CONT (Figure 1b)	1	174	54	18	10	0.0147	Right inferior frontal gyrus
CONT Age > 22qDS age (Figure 2b)	1	189	66	−48	−4	0.00837	Right middle temperoccipital cortex
22qDS Age > CONT age (Figure 2b)	1	284	24	6	−24	2.76E-04	Right temporal pole/parahippocampal gyrus
	2	163	34	32	−12	0.00233	Right lateral frontal cortex
22qDS participants only, SRS (Figure 3)	1	405	10	40	−4	1.19E-07	Anterior cingulate/paracingulate gyrus
	2	277	26	62	−2	2.03E-05	Right lateral frontal cortex
	3	250	12	66	24	6.38E-05	Right medial frontal cortex
	4	179	−12	72	10	0.00162	Left medial frontal pole
CONT > 22qDS (med exclusion) (Supplementary Figure S3)	1	498	0	−60	32	5.96E-08	Precuneus
	2	462	−22	48	12	2.38E-07	Frontal pole

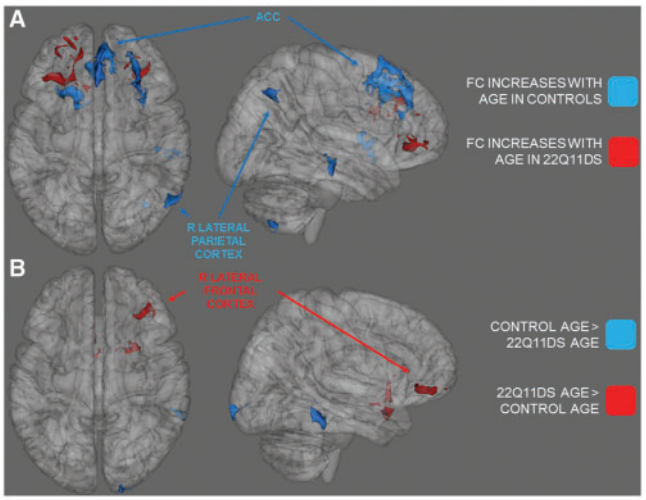

Fig. 2 Developmental effects on PCC connectivity. Figure 2a depicts brain regions in which greater functional connectivity with the PCC is associated with increasing age in 22q11DS patients [red—right (R) vmPFC, left (L) frontal cortex] and controls [blue—paracingulate gyrus, anterior cingulate gyrus (ACC), R superior frontal gryus, L putamen, R lateral temporal cortex, R lateral parietal lobe, R cerebellum]. Figure 2b depicts regions in which there is a significant age × diagnosis interaction [i.e. differential PCC connectivity with increasing age for 22q11DS patients (22q11DS) *vs* controls (Cont)]. Red colors indicate regions in which there is differentially increased connectivity in 22q11DS patients (R vmPFC, Subcallosal cortex, R orbitofrontal cortex), whereas blue colors indicate differentially increased PCC functional connectivity with increasing age in controls (Cont—occipital pole, R lateral temporal cortex).

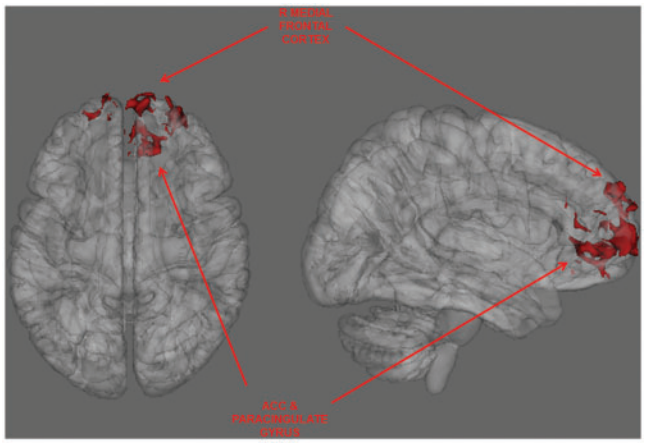

Fig. 3 Association between PCC connectivity and SRS. Regions in which PCC connectivity is significantly associated with a lower SRS score in 22q11DS patients. As shown, connectivity between the PCC and diffuse frontal regions, including the vmPFC, is associated with a lower SRS score (and hence, improved social functioning) in 22q11DS.

above were re-run excluding any subjects currently taking antipsychotic, psychostimulant or antidepressant medications (11 patients, 2 controls). The observed group differences remained significant, with controls displaying significantly greater FC than 22q11DS participants between the PCC seed and the frontal pole (Supplementary Figure S3). Correlations between the PCC and vmPFC seed regions remained significantly stronger for controls relative to 22q11DS participants ($P = 0.0132$). Regarding age effects, controls continued to show increased PCC connectivity to the ACC, right lateral parietal and superior frontal cortex with increasing age. However, the age × diagnosis interaction effects changed slightly upon removal of medicated subjects. Specifically, differential age-associated increases in FC with the PCC in controls no longer reached the threshold for statistical significance. In contrast, relative to controls, patients showed differential age-associated increases in connectivity between the PCC and right inferior temporal cortex. Finally, the observed association between increased PCC to frontal connectivity and lower SRS scores remained significant, after excluding 22q11DS participants on medications.

DISCUSSION

22q11DS is a recurrent genetic mutation associated with defects in cortical circuit formation and high rates of neuropsychiatric disorders characterized by marked social impairment. Evidence from animal models of 22q11DS suggests that disruptions in long-range neural synchrony may be a fundamental component of the disorder (Sigurdsson *et al.* 2010); nevertheless, very little is known about the functional architecture of the resting brain in human subjects with 22q11DS. Using a seed-based approach, we observed a pattern of reduced long-range connectivity between the PCC and other DMN nodes in 22q11DS participants, consistent with a 'developmental disconnection' model of the disorder. Furthermore, the strength of PCC-frontal connectivity was associated with increased social competence, thus linking integrity of DMN connectivity with social behavior in 22q11DS. As default network regions are implicated in social information processing and internal representations of self (Uddin *et al.*, 2007), our findings offer new evidence that within-network robustness is an integral

factor in modulating the severity of the behavioral phenotype in 22q11DS.

Our findings accord with recent neuroimaging and electrophysiological studies in adults with idiopathic autism spectrum disorders, which have revealed a pattern of altered intrinsic connectivity of long-range DMN circuitry (Murias *et al.*, 2007; Kennedy and Courchesne, 2008). The majority of studies of adolescents and adults with ASD have found reduced functional connectivity of the DMN (Kennedy and Courchesne, 2008; Assaf *et al.*, 2010; Weng *et al.*, 2010); however, a recent study of children with ASD found a pattern of hyper-connectivity of the PCC with medial and anterolateral temporal cortex as well as local hypo-connectivity within posteromedial corte × (Lynch *et al.*, 2013) suggesting that the pattern of DMN alterations in idiopathic ASD may vary as a function of developmental stage (Di Martino *et al.*, 2009b). A meta-analysis of the functional neuroimaging literature also indicated that the PCC is consistently hypo-activated in social tasks in idiopathic ASD relative to typically developing individuals (Di Martino *et al.*, 2009a), suggesting a neural basis for self-referential processing deficits in both task-positive and task-negative (i.e. resting state) contexts. Moreover, our observed association between long-range DMN connectivity and social behavior in 22q11DS is consistent with a previous study in healthy adults (Di Martino *et al.*, 2009b), reporting that lower levels of autistic traits, as assessed by the SRS, were related to increased FC between the pregenual ACC and anterior mid-insula, brain regions important for social processing previously shown to be hypo-active in ASD patients (Di Martino *et al.*, 2009a). Collectively, these findings support the notion that DMN integrity may be a candidate marker of social competence, in both clinical and non-clinical populations.

Our results are also consistent with those of animal models of 22q11DS, which have reported dramatically reduced neural synchrony between anatomically distant brain regions, suggesting a cellular basis for our findings of disrupted long-range FC (Sigurdsson *et al.*, 2010). In the mouse model, reduced hippocampal-prefrontal synchrony was associated with working memory deficits; a core feature of psychosis. The contribution of disrupted connectivity to other aspects of the phenotype (i.e. social deficits) has not yet been explored in the 22q11DS mouse model, but would be an important extension of this study.

As our sample included a large proportion of young children, we did not see a high rate of psychotic disorder in our sample, and thus we did not analyze DMN activity as a predictor of psychotic symptoms; this is an active area of investigation for our future longitudinal studies. Multiple studies have now been conducted indicating aberrant network connectivity, both in the DMN and globally, in patients with idiopathic schizophrenia as well as their first degree relatives, indicating that altered FC during rest may be associated with genetic risk for the illness (Whitfield-Gabrieli and Ford, 2012; Williamson and Allman 2012; Alexander-Bloch *et al.*, 2013). Remarkably consistent with our findings, (Woodward *et al.*, 2011.) recently reported increased connectivity between the PCC and the left IFG—a brain region typically considered part of the salience network—in patients with schizophrenia relative to controls, suggesting that the functional topography of the DMN may be similarly altered in patients with idiopathic schizophrenia and 22q11DS.

To our knowledge, only one prior study of resting state fMRI in 22q11DS has been conducted (Debbane *et al.*, 2012). Using independent components analysis, an exploratory data-driven approach to analysis of resting-state fMRI data that is an alternative to model-based (ROI) approaches, Debbane *et al.* (2012) identified group differences in several networks, including the DMN. Interestingly, their findings are largely congruent with those reported here, with 22q11DS participants showing greater connectivity to diffuse frontal regions not typically considered part of the DMN, and controls exhibiting stronger connectivity between frontal and posterior regions such as the precuneus and PCC. This study also reported associations between altered connectivity and psychotic symptom severity (Debbane *et al.*, 2012). In contrast, our analysis focuses on a dimensional indicator of social behavior, which is likely to cut across multiple diagnostic categories involving social impairment (i.e. psychosis and ASD).

The strength of FC within DMN nodes may rely on underlying structural connectivity between brain regions. Diffusion tensor imaging studies have identified reduced white matter integrity in long-range fiber tracts in 22q11DS (see Schreiner *et al.*, 2012 for a review), suggesting altered white matter microstructure in tracts connecting these brain regions. Notably, a recent study of healthy adolescents found that FC between the mPFC and PCC depends upon the maturation of the underlying cingulum white matter tract, suggesting that structural connectivity defects may contribute to the observed reductions in functional connectivity in 22q11DS participants (Gordon *et al.*, 2011). Multimodal imaging studies are now underway, in order to address this question.

The wide age range and relatively large number of typically developing controls in our study allowed us to investigate developmental effects on resting state connectivity. The differential increase in connectivity between the PCC and right lateral temporal cortex evident in controls is consistent with previous literature indicating increases in long-range connectivity within the DMN with maturation (Supekar *et al.*, 2010). In contrast, 22q11DS participants showed evidence of more diffuse frontal connectivity with the PCC, to regions outside of the classic DMN, with increasing age. These findings suggest an altered developmental trajectory of resting state network development in 22q11DS, which may be relevant to the emergence of psychopathology in adolescence. However, given that medication status had an impact on the age × diagnosis interaction results, further investigation is needed. Prospective longitudinal studies are required in order to confirm the intriguing possibilities raised by our cross-sectional findings.

These findings must be interpreted in the light of several caveats. First, we chose to use global signal regression (GSR) in order to account for sources of any physiological, non-neuronal noise in the data. Previous studies have raised the concern that adjusting for global signal may artificially induce, or inflate the strength of, negative functional correlations in resting state networks (Cole *et al.*, 2010); however, there is no currently accepted consensus in the field on whether or not to apply GSR to rs-fMRI data. Given these concerns, and to avoid such interpretive difficulties regarding anticorrelations, we focused our analyses only on positive correlations. Second, the possibility of differential motion between experimental groups has become a growing concern for interpretation of group differences in resting-state data (Power *et al.*, 2012). Though there are limitations to any method of addressing this, we used a conservative threshold for motion exclusion and ensured that there were no differences in motion between diagnostic groups. Thus, motion artifacts are not likely to account for the observed group differences in connectivity patterns. Finally, the two diagnostic groups differed significantly in terms of Full Scale IQ. Intellectual disability is a known and well-characterized aspect of the 22q11DS phenotype, and prior rs-fMRI studies in 22q11DS and other cognitive impaired populations (e.g. idiopathic schizophrenia) have typically not accounted for IQ differences (Yu *et al.*, 2011; Debbané *et al.*, 2012). In this context, IQ is considered a group defining variable and thus could not be included in our group comparison models (Ho *et al.*, 2012). Thus, we cannot rule out the possibility that variability in IQ may have had an effect on the results of group comparisons. The relationship between IQ and DMN connectivity is a complex developmental issue, which warrants further consideration in future studies

including both 22q11DS patients and other neurodevelopmental disorders. However, it is important to note that SRS scores were not associated with IQ 'within' our 22q11DS sample, and thus could not account for the within-group relationships observed.

In summary, this study reveals dysfunction in long-range connectivity within DMN regions in 22q11DS, a recurrent genetic mutation associated with abnormal neuronal migration and high rates of schizophrenia and ASD. Consistent with previous findings in the general population (Di Martino *et al.*, 2009b), we found that increased long-range connectivity in 22q11DS was associated with the SRS, a continuous measure of autistic traits, suggesting that: (i) DMN circuitry is a clinically relevant locus of dysfunction in this syndrome, which may have predictive validity for subsequent development of psychopathology and (ii) that alterations in FC identified in the context of this syndrome may fall on a continuum with the broader population. Future translational investigations in both human and animal models will clarify the contributions of specific genes within the 22q11.2 locus to the observed disruptions in neural connectivity.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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