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Divergent default mode network connectivity during social perception in 22q11.2 deletion syndrome

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ABSTRACT

Aim: The 22q11.2 deletion (22q11DS) syndrome is a neurogenetic condition marked by social dysfunction. A major network involved in social cognition is the default mode network (DMN). To date, no study has investigated DMN functional connectivity during socio-cognitive paradigms in 22q11DS.
Method: We used the psychophysiological analysis (PPI) to investigate functional connectivity of the DMN during social perception in 22 participants with 22q11DS and 22 healthy controls. Association between DMN connectivity and prodromal symptoms was also examined.
Results: 22q11DS patients exhibited stronger connectivity between the inferior parietal lobule (IPL) and the posterior cingulate cortex (PCC)/precuneus as well as lower connectivity between the precuneus and middle/superior frontal regions compared to controls. Association between IPL-PCC/precuneus connectivity and negative symptoms was also found in individuals with 22q11DS.
Conclusion: Our results point to (1) divergent DMN connectivity in patients with 22q11DS compared to controls; (2) association between DMN connectivity and negative symptom severity in patients. Results support the role of the DMN in social deficits of the 22q11DS population.

1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is a genetic disorder affecting approximately 1 in 1000–2000 fetuses (Shprintzen, 2008; Grati et al., 2015) and accounting for 1–2% of schizophrenia cases (Karayiorgou et al., 2010). Various clinical features ranging from somatic, cognitive to psychiatric manifestations characterize the 22q11DS phenotype. Additionally, the syndrome is marked by social cognition deficits (Campbell et al., 2010; Campbell et al., 2011; Shashi et al., 2012; Ho et al., 2012; Jalbrzikowski et al., 2012; Gur et al., 2014; Badoud et al., 2017) that have been shown as related to social functioning deficits (Campbell et al., 2015; Shashi et al., 2012) and negative symptoms emergence (Ventura et al., 2009; Lincoln et al., 2011).

A major brain network involved in social cognition is the default mode network (DMN). In healthy populations, the DMN has been found activated during a range of cognitive tasks, including socio-cognitive tasks (Andrews-Hanna et al., 2014; Spreng and Grady, 2010). The DMN is thought to encompass a set of regions including the medial prefrontal cortex (MPFC), the posterior cingulate cortex (PCC)/precuneus, the inferior parietal lobule (IPL), lateral temporal cortex (LTC), and anterior cingulate cortex (ACC) (Grecucci et al., 2013; Spreng et al., 2009). As in schizophrenia, studies conducted in the 22q11DS population point to divergent functional connectivity within the DMN (Padula et al., 2017; Mattiaccio et al., 2016; Padula et al., 2015a, 2015b; Schreiner et al., 2014; Debbané et al., 2012). The DMN has been defined as a brain system that is deactivated during cognitive tasks but activated during resting-state or without engagement in a specific task (Raichle et al., 2001). To date, DMN connectivity has only been investigated during resting-state in the 22q11DS population. While some studies showed decreased DMN connectivity in participants with 22q11DS (Padula et al., 2017; Mattiaccio et al., 2016; Padula et al., 2015a, 2015b; Schreiner et al., 2014); others found opposite findings (Debbané et al., 2012). More specifically, Schreiner et al. (2014) and Padula et al. (2015a, 2015b, 2017) found reduced functional connectivity (FC) between the anterior and posterior part of the DMN during resting-state, whereas in Debbané et al. (2012), both increased and reduced DMN connectivity was reported. Indeed, authors showed reduced FC of the DMN in 22q11DS compared to healthy controls in the medial frontal gyrus, cingulate gyrus, superior frontal gyrus, but increased connectivity of the middle frontal gyrus, inferior parietal

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lobule, superior frontal gyrus, and cuneus in participants with 22q11DS compared to controls. More recently, Mattiaccio et al. (2016) also reported increased DMN connectivity involving the superior parietal lobule. Some of those previous studies also found significant associations between DMN connectivity and clinical measures. Debbané et al. (2012) reported that increased connectivity of the DMN was associated with a reduction of some psychotic symptoms (expression of emotion, suspicious/persecutory ideas, disorganized communication), whereas Schreiner et al. (2014) found that increased strength of long-range DMN connectivity was related to improved social functioning in participants with 22q11DS. Taken together, these studies clearly demonstrate divergent FC of the DMN during resting-state in 22q11DS. Despite the crucial role of the DMN in social cognition and the importance of social cognition deficits in 22q11DS, DMN connectivity during socio-cognitive tasks has never been investigated in this population. However, functional connectivity allows to examine how large-scale distributed neural systems are temporally correlated during specific tasks and provides a new insight into the brain's anatomical organization and how such organization may be impaired in psychopathology. Such an approach would, thus, be needed to better understand how the DMN is organized to support socio-cognitive processes.

A lower-order process of social cognition called social perception has been hypothesized to support others aspects of social cognition (Mier et al., 2010). Indeed, social perception is thought to provision the understanding of emotions, actions, and intentions of others through the initial processing of gaze direction, body movements, hand gestures, facial expressions, and other biological-motion cues (Allison et al., 2000). In a previous study from our group, BOLD activation was investigated during social perception and divergent activation in regions belonging to the DMN was identified in participants with 22q11DS compared to healthy controls (Dubourg et al., 2018). Based on these findings, the current study aims to examine whether FC of the DMN differs during social perception in participants with 22q11DS. We predicted that individuals with 22q11DS would show divergent DMN connectivity during social perception compared to healthy controls. Additionally, given that social cognition is associated with social functioning and might contribute to negative symptoms expression, we aimed to examine whether DMN connectivity strength could be related to social functioning deficits and negative symptom severity.

2. Methods

2.1. Participants

Participants were recruited through parent associations or word of mouth and were tested in our research laboratory during an ongoing longitudinal study. Twenty-two participants with 22q11DS aged between 12 and 32 years were included (mean age = 20.3 ± 5, 17 (77%) females). The presence of a 22q11.2 microdeletion was confirmed in all participants using quantitative fluorescent polymerase chain reaction (QF-PCR). Participants diagnosed with a DSM-IV psychotic disorder were excluded from this study ($n = 2$) to decrease the influence of confounding factors on brain activation patterns (e.g. long-term use of antipsychotics). However, some participants met formal diagnostic criteria for other current psychiatric conditions, and 10 participants were under medication at the time of testing (see Table 1). Furthermore, 22 controls including siblings ($n = 13$) and unrelated individuals ($n = 9$) aged between 12 and 32 (mean age = 19.7 ± 5, 15 (68%) females) were also included (see Table 1) and were screened for the presence of any neurological problems, and psychological or learning difficulties.

Written informed consent was obtained from all participants and their parents under protocols approved by the Swiss Ethics Committee on research involving humans.

2.2. Clinical assessment

The presence of psychiatric disorders was assessed in adolescents below 18 years using the Diagnostic Interview for Children and Adolescents – Revised (Reich, 2000), and the mood and psychosis supplement of the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL(Kaufman et al., 1997). Adult participants were screened using the Structured Clinical Interview for DSM-IV axis disorders (SCID-I; First, 1996). Participants were also screened for positive and negative symptoms of psychosis using the Positive And Negative Syndrome Scale (PANSS, Kay et al., 1987). The PANSS is composed of a positive, negative and general psychopathology subscale. All symptoms are rated on a 7-point severity scale (ranging from 1 to 7).

2.3. Intellectual functioning

All participants completed the Wechsler Intelligence Scale for Children III or IV (WISC-III-R; Weschsler, 1991 or WISC-IV-R; Weschsler, 2005) or Adult III or IV (WAIS-III; Weschsler, 1997 or WAIS IV; Weschsler, 2008) in order to obtain an evaluation of global intellectual functioning. Mean full-scale IQ was 74 (SD = 12) in participants with 22q11DS and 118 (SD = 11) in controls.

2.4. Social functioning

We administered the Adaptive Behavior Assessment System II (ABAS II; Harrsion and Oakland, 2003) to parents of all participants. The ABAS is a measure of adaptive behavior and skills. The questionnaire measures three general domains: Conceptual, Social, and Practical. The ABAS contains 193 items rated on a 4-point scale, with 0 = is not able, 1 = never when needed, 2 = sometimes when needed, 3 = always or almost when needed. Because our hypotheses were specifically related to social functioning, we only used the social domain.

2.5. Experimental design

The experiment consisted of 2 runs during which participants were presented with positive and negative images from the International Affective Picture System (IAPS; Lang et al., 2005) and scrambled versions of the latter images (obtained using the Photoshop plugin (http://www.telegraphics.com.au/sw/product/Scramble). Participants were instructed to indicate whether the image was intact or scrambled using an MRI-compatible response box. Target images were divided in 4 categories using a 2 (social content) × 2 (valence) factorial design: social & positive valence, social & negative valence, non-social & positive valence, and non-social & negative valence (Fig. 1). For additional information regarding the experimental design, see (Dubourg et al., 2018).

2.6. Data acquisition and analysis

Structural and functional images were acquired using a Siemens Prisma 3T scanner at the Geneva Center for Biomedical Imaging (CIBM). fMRI data were processed using Statistical Parametric Mapping 12 (SPM12; Welcome Department of Neuroscience, London UK). For details regarding the acquisition protocol see Dubourg et al. (2018). fMRI data were processed and analysed using Statistical Parametric Mapping 12 (SPM12; Welcome Department of Neuroscience, London UK). Functional images were realigned using rigid body registration and resliced. Participants with motion exceeding 3 mm in any of the 6 directions were not included in the analyses (4 patients and 2 controls).

Each participant's structural image was coregistered to the mean of the realigned functional images and segmented with the Dartel option to obtain tissue classification. Finally, we normalized to 1 mm^3

Table 1
Demographic information for 22q11DS and healthy control participants.

			Diagnostic group 22q11DS	Controls	Comparison Anova	*p*-value
n			22	22		
Age			20.3 (± 5.2)	19.7(± 5.1)	0.120	0.730
Gender (% of female)			17 (77%)	15 (68%)	0.442	0.510
Full IQ (mean (SD))			74 (± 12)	118 (± 11)	162.8	<0.01
ABAS (mean (SD))			51.4 (± 9.4)	60.8 (± 5.5)	9.9	0.004
PANSS positive (mean (SD))			10.1 (± 3.2)	/		
PANSS negative (mean (SD))			20.5 (± 5.4)	/		
Psychiatric diagnosis (*n* (%))		Major depression disorder	5 (23%)			
		Specific phobia	3 (13%)			
		Simple phobia	1 (4%)			
		Generalized anxiety disorder	3 (13%)			
		Obsessive compulsive disorder	1 (4%)			
		Alcohol dependence	1 (4%)			
		Oppositional defiant disorder	1 (4%)			
		Delusions	2 (8%)			
		ADHD	3 (13%)			
Psychotropic medication	Categories	Antipsychotics	1 (4%)			
		Antidepressants	7 (32%)			
		Methylphenidate	4 (18%)			

ABAS, Adaptive Behavior Assessement System.

Montreal Neurologic Institute (MNI) space and spatially smoothed with a 6-mm at full-width half-maximum three-dimensional Gaussian kernel, employing the diffeomorphic anatomical registration using exponential lie algebra algorithm (DARTEL).

In our previous fMRI study, all main effects and interactions of the 2 × 2 design were investigated (Dubourg et al., 2018). Based on these results, we defined seed regions for subsequent psychophysiological analysis (PPI). The PPI analysis aims to measure functional connectivity between a seed region and each voxel in the whole brain during an experimental task. In this current study, we particularly focused on the contrast of interest: social versus non-social images, given the divergent pattern of activation observed between individuals with 22q11DS and healthy controls in our previous study (Dubourg et al., 2018). At the first level, the social and non-social conditions were entered in a general linear model and contrast images were generated for each participant using the estimated GLM parameters (social vs. non-social). These individual contrast images were then included in an independent two-sample *t*-test at the group level to determine significant brain activation in participants with 22q11DS versus healthy controls. In so doing, age, gender, handedness, IQ, as well as medication were entered as covariates. The emerging main task effect of group was subsequently tested at a primary voxel-level statistical threshold of $p < 0.001$ (uncorrected, whole brain) and $k \geq 20$. For clusters that survived this threshold at the voxel level, a cluster-extent family-wise correction (FWEc) for multiple comparisons at $p < 0.05$ was applied.

2.6.1. Regions of interest

Regions of interest were defined based on peak coordinates of the main task effect (social versus non-social). It appears that the functional organization of the cortex is not identical across human beings, which can lead to inter-individuals differences in functional anatomy. For this reason, we decided to select voxels for each subject with the strongest task effect, an approach that allows to take into consideration inter-individual differences in functional anatomy and appears to be the most sensitive approach (O'Reilly et al., 2012). We defined 5 ROIs belonging to the DMN showing decreased activity in participants with 22q11DS compared to controls during the social (versus non-social) perception condition. Spheres with a 6 mm radius were then defined around the peak of the following ROIs: the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), the inferior parietal lobule (IPL), the posterior cingulate cortex (PCC), and the precuneus.

Fig. 1. Example of stimuli (from the International Affective Picture System). Left to right: negative, positive and scrambled. Top panel: social, bottom panel: non-social.

Table 2
Group comparison of significant PPI effects during social versus non-social contrast.

Seed regions	k	t	MNI (x,y,z)			H	Region	BA
22q11DS > CTRL								
IPL	989	5.54	24	−60	19	R	Posterior cingulate	31
		4.17	22	−64	27	R	Precuneus	7
		3.87	19	−68	23	R	Precuneus	31
		3.75	17	−67	28	R	Precuneus	31
		3.45	30	−64	21	R	Middle temporal gyrus	39
CTRL > 22q11DS								
Precuneus	1984	6.59	33	12	61	R	Middle frontal gyrus	6
		5.95	30	−2	65	R	Middle frontal gyrus	6
		4.71	32	22	57	R	Superior frontal gyrus	8

Coordinates of peak effects are provided in MNI space, Montreal Neurological Institute, H, Hemisphere, BA, Brodman area.

2.6.2. Connectivity analysis

The PPI term was estimated as the first eigenvariate of the extracted BOLD signal of the seed volume of interest (VOI) for each subject. This term corresponds to the average BOLD signal of the extracted VOI using the VOI extraction function in SPM. Hemodynamic deconvolution was performed on the extracted time series to remove the effects of the canonical hemodynamic response function (HRF).

The extracted time series were multiplied by the psychological variable (demeaned time course of the task) and reconvolved with the HRF to obtain the PPI interaction. The time series were not corrected for the effect of any variable, as potential confounds were factored into the previous stage of data regression.

The psychological, physiological, and interaction term were entered into a general linear model for each subject with the interaction term as regressor of interest. These individual results were used to determine difference in connectivity per group and were then included in an independent two-sample *t*-test to examine differences between individuals with 22q11DS and healthy controls. Voxels showing a group difference in connectivity between the seed VOI and the rest of the brain are reported in Table 2.

All statistical maps were threshold at $p < 0.001$ (uncorrected, whole brain) and $k \geq 20$. For voxels that survived this threshold at the peak level, a cluster-extent family-wise correction (FWEc) for multiple comparisons at $p < 0.05$ was applied.

Correlation analyses were performed to determine whether connectivity observed in participants with 22q11DS was related to clinical variables including: social functioning as well as symptom severity (positive and negative symptoms). Connectivity was assessed by extracting the first eigenvariate time series from a 6 mm radius sphere from the regions showing significant correlation with the seed region. The ABAS scores, PANSS positive and negative were used for this analysis. Spearman partial correlation with age, gender, and IQ were conducted. Multiple comparison correction using the Benjamini-Hochberg procedure was applied.

3. Results

3.1. BOLD activity during social versus non-social perception

In our previous study (Dubourg et al., 2018), the social vs. non-social contrast revealed hypoactivation in the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), inferior parietal lobule (IPL), posterior cingulate cortex (PCC) and precuneus regions in patients compared to controls (see Fig. 2).

3.2. PPI effects during social versus non-social perception

Within-group results for the contrast of interest (social versus non-social perception) are displayed in the supplementary material (See Tables 1 and 2 of the supplementary material).

The between–group comparison of PPI effects during social perception (social vs. non-social images) showed that compared to the control group, individuals with 22q11DS exhibited stronger functional connectivity between the right IPL and PCC/precuneus but weaker functional connectivity between the right precuneus and middle/superior frontal regions (see Table 2 and Fig. 3).

In order to determine the nature of this effect, between-group two-sample test for each condition separately (social and non-social) were conducted. Results revealed that individuals with 22q11DS showed stronger connectivity strength between the right IPL and PCC/precuneus as well as between the right precuneus and the left middle frontal gyrus during the perception of social images (See Table 3). During the perception of non-social images, results revealed that healthy controls exhibited stronger functional connectivity between the right precuneus and the left inferior/superior parietal lobule compared to individuals with 22q11DS (See Table 4)

3.3. Association with clinical variables

In the group of participants with 22q11DS, a negative correlation between IPL<->PCC/precuneus connectivity strength and the PANSS negative subscale ($r = -0.71$, $p = 0.001$) was observed (See Fig. 4). Nevertheless, five individuals with 22q11DS received a diagnosis of depression in our sample. To ensure that the observed result was not driven by patients with a diagnosis of depression, we re-conducted this analysis after removing patients with a diagnosis of depression. Results remained unchanged, as a significant and negative association between IPL-PCC/precuneus connectivity and negative symptom severity was observed ($r = -672$, $p = 0.006$). No significant correlation between PPI activity and the PANSS positive subscale or the ABAS social domain was observed (all $p < 0.05$). Results remained significant after multiple comparison correction.

4. Discussion

This study is the first attempt to investigate the functional architecture of the default-mode network (DMN) during a socio-cognitive task in 22q11DS. As the DMN is involved in social information processing (Uddin et al., 2007), it is likely that divergent connectivity within this network could contribute to social deficits frequently observed in this syndrome. Using a seed-based approach, we observed a divergent pattern of DMN connectivity during social information perception in 22q11DS compared to controls. We found stronger functional connectivity (FC) between the right IPL and the PCC/precuneus as well as weaker FC between the right middle frontal cortex and the precuneus in the 22q11DS group compared to controls during social versus non-social image perception. Furthermore, the strength of ILP-PCC/precuneus connectivity was associated with increased severity of negative symptoms in 22q11DS. Taken together, our findings bring new evidence on the role of the DMN in 22q11DS.

4.1. Within DMN divergent connectivity

We found group differences in connectivity strength during social compared to non-social image perception. We observed stronger FC between the PCC (extending to the precuneus) and the IPL in 22q11DS compared to controls. Given the results obtained for the individual conditions (social or non-social image perception separately), this result appears to be explained by the fact that 22q11DS individuals exhibit higher FC between IPL and PCC/precuneus during the visualization of social images compared to healthy controls. These regions are considered as “core-self” nodes of the DMN. This notion of a “core-self” node particularly holds true for the PCC, given its highest level of metabolic activity and connectivity compared to others DMN regions (Hagmann et al., 2008; Leech and Sharp, 2014; Tomasi and Volkow,

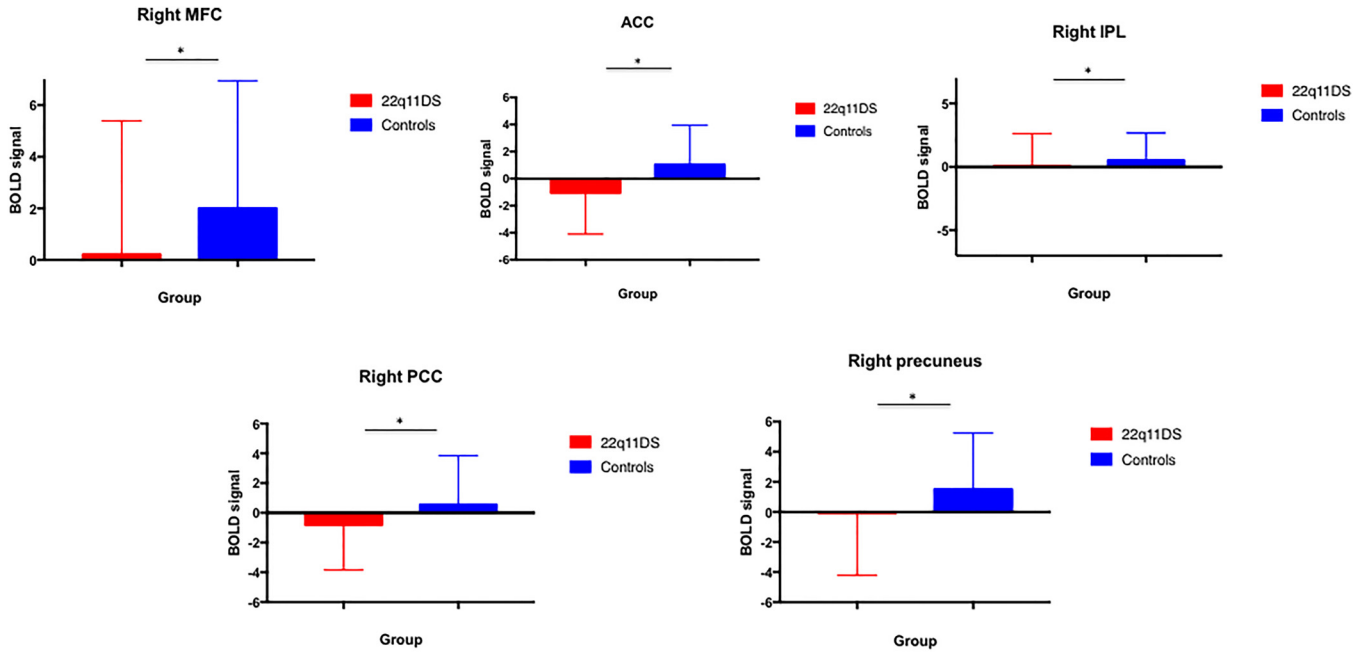

Fig. 2. Level of BOLD signal activity in regions showing interaction differences during social (versus non-social) perception in participants with 22q11DS compared to healthy controls (* cluster-extent family-wise correction (FWEc) for multiple comparisons, $p < 0.05$).

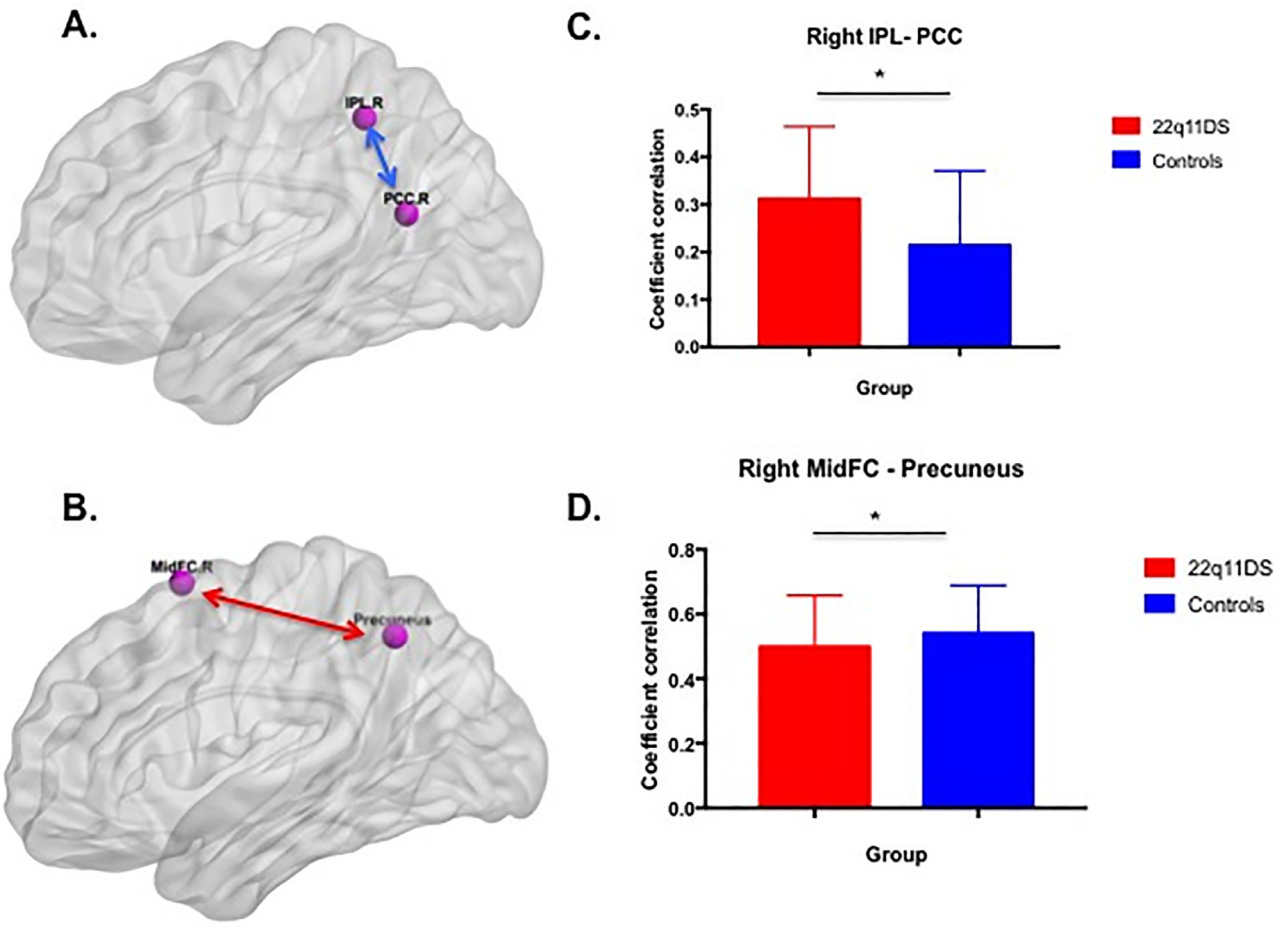

Fig. 3. Illustration of the psychophysiological results during social versus non-social contrast showing the seeds regions and the regions co-activated visualized with BrainNet Viewer (http://www.nitrc.org/projects/bnv/), (Xia et al., 2013) **(A, B).** Partial correlation obtained by extracting time courses in a sphere of 6 mm radius for each region of interest revealed stronger correlation strength between the right IPL and PCC; (C) and a weaker correlation strength and the right MidFC and precuneus (D) in the 22q11DS group compared to controls (* cluster-extent family-wise correction (FWEc) for multiple comparisons cluster, $p < 0.05$).

Table 3
Group comparison of significant PPI effects during social image perception.

Seed regions	k	t	MNI (x,y,z)			H	Region	BA
22q11DS > CTRL								
Precuneus	728	4.37	−41	6	47	L	Middle frontal gyrus	6
		4.10	−37	−67	50	L	Middle frontal gyrus	6
		4.04	−32	4	60	L	Middle frontal gyrus	6
IPL	854	5.68	24	−60	19	R	Posterior cingulate	31
		3.86	22	−64	27	R	Precuneus	7
		3.77	34	−66	22	R	Middle temporal gyrus	39

Coordinates of peak effects are provided in MNI space, Montreal Neurological Institute, H, Hemisphere, BA, Brodman area.

Table 4
Group comparison of significant PPI effects during non-social image perception.

Seed regions	k	t	MNI (x,y,z)			H	Region	BA
CTRL > 22q11DS								
Precuneus	709	4.23	−38	−59	54	L	Superior parietal lobule	7
		3.89	−40	−55	45	L	Inferior parietal lobule	40
		3.75	−35	−52	38	L	Inferior parietal lobule	40
	706	4.41	39	−50	61	R	Inferior parietal lobule	40
		4.24	47	−42	57	R	Inferior parietal lobule	40

Coordinates of peak effects are provided in MNI space, Montreal Neurological Institute, H, Hemisphere, BA, Brodman area.

2011). Impaired connectivity between the PCC and other DMN regions has been largely demonstrated in psychiatric population characterized by social deficits. Indeed, in Autism Syndrome Disorder (ASD) (See Hull et al., 2017 for a review), schizophrenia (See Hu et al., 2016 for a review) but also in previous resting-state investigations conducted in 22q11DS (Padula et al., 2015a, 2015b; Padula et al., 2017; Schreiner et al., 2014), decreased FC between the PCC and additional DMN regions has been pointed out. In a recent review, it has been demonstrated that PCC is particularly sensitive to emotional engagement and that connectivity changes between the PCC/precuneus and regions inside or outside the DMN occurs during emotion perception (Li et al., 2014). One study conducted in ASD previously reported divergent connectivity between the PCC/precuneus and IPL like in the present study (Wiggins et al., 2011). However, while authors reported weaker FC between these regions, we observed stronger functional connectivity between the PCC/precuneus and the IPL during social versus non-social perception in our 22q11DS population. Nevertheless, as BOLD signal was reduced in both regions in 22q11DS participants compared to controls, our result suggest stronger deactivation of these regions during social compared to nonsocial image perception. Most studies investigating FC do not report BOLD signal in results section (see for example, Schreiner et al., 2014; Wiggins et al., 2011), which increases the risk of misinterpretation of the obtained findings. Indeed, stronger FC is generally interpreted as an indicator of better FC between brain regions. However, when the regions are hypo-activated compared to the comparison group (as it was the case in the present study), stronger FC reflects more pronounced deactivation between these regions. This highlights that higher connectivity between brain regions cannot be automatically considered as better connectivity. In particular, the literature has demonstrated an activity balance of the DMN depending of the nature of the task. Indeed, while the DMN appears to be deactivated during goal-directed cognitive tasks, the DMN has been shown to be more activated during internal processes including socio-cognitive tasks (Raichle et al., 2001). Thus, stronger deactivation of the DMN during social images perception should be interpreted as an abnormal pattern of connectivity. Therefore, it is unclear from previous studies that did not report BOLD signal values whether the obtained results have been correctly interpreted. Future studies focusing on functional connectivity investigation should report BOLD activity to ensure the accuracy of their interpretation.

4.2. Within and outside DMN divergent connectivity

Our study also pointed out weaker connectivity between the right precuneus and the middle frontal cortex in 22q11DS compared to healthy controls during social perception. Indeed, as the within-group analysis pointed out (See supplementary material), healthy participants showed increased FC between these regions compared to 22q11DS individuals during social perception. Previous findings using resting-state imaging demonstrated opposite patterns, meaning higher FC between frontal regions, not considered to be part of the DMN, and posterior regions, such as the precuneus, in individuals with 22q11DS compared to healthy participants (Mattiaccio et al., 2016; Schreiner et al., 2014). However, our current study focused on FC during social perception, which could explain these divergent findings. Moreover, one study highlighted that subregions of the precuneus present different pattern of FC (Zhang and Li, 2012). While the dorsal/anterior and dorsal/posterior precuneus seem particularly implicated in guided behaviors and mental imagery (Hanakawa et al., 2003; Knauff et al., 2003; Malouin et al., 2003; Ogisoet al., 2000; Suchan et al., 2002), the ventral precuneus mainly plays a role in socio-cognitive processes (Cavanna and Trimble, 2006; den Ouden et al., 2005; Farrow et al., 2001; Kircher et al., 2002; Ochsner et al., 2004; Ruby and Decety, 2001). Thus, resting-state and socio-cognitive tasks could recruit different subregions of the precuneus, which could explain divergence with previous findings in 22q11DS. Future studies delineating the FC within precuneus subregions should be conducted.

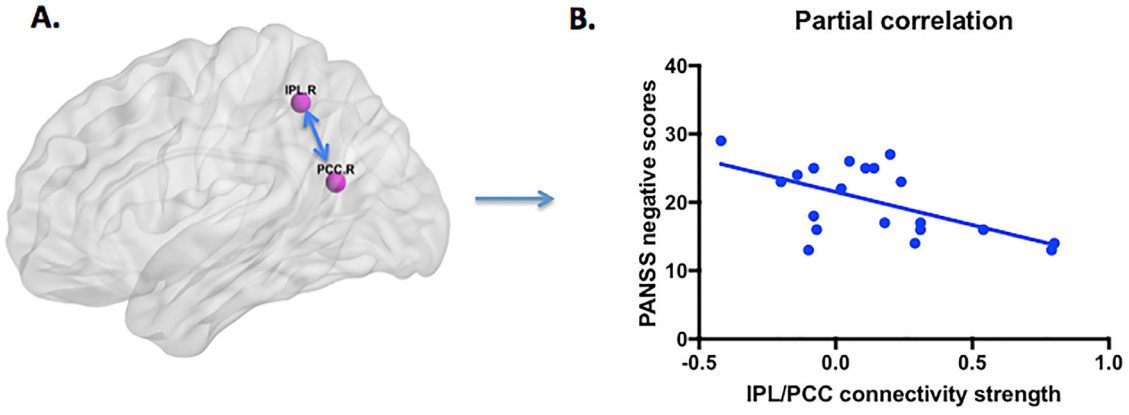

Fig. 4. (A) Significant interaction between the IPL and PCC/precuneus during social versus non-social perception (B) Correlation between IPL-PCC/precuneus connectivity strength during social versus non-social perception and PANSS negative scores.

4.3. DMN and social cognition

Our results are consistent with neuroimaging studies highlighting the role of the DMN during socio-cognitive processes. Indeed, in several populations marked by social impairments, such as ASD or schizophrenia, impaired connectivity of the DMN during social processing (emotion or face processing) (Das et al., 2005; Rudie et al., 2012) has been reported. In the 22q11DS, social cognition deficits appear to be a main characteristic of the phenotype (Campbell et al., 2010; Campbell et al., 2011; Shashi et al., 2012; Ho et al., 2012; Jalbrzikowski et al., 2012; Gur et al., 2014; Badoud et al., 2017). Recently, a review on social cognition demonstrated that 22q11DS individuals have impaired emotion processing and complex theory of mind compared to their peers while other aspects of social cognition have been barely examined, in particular social perception (Norkett et al., 2017). However, social perception has been hypothesized to be a key component of social cognition supporting others socio-cognitive processes. DMN dysconnectivity during social perception might thus represent a marker for social cognition impairments observed in the 22q11DS population.

Moreover, in both clinical and non-clinical populations, DMN integrity has been hypothesized as a marker for social competences (Schreiner et al., 2014). An association between long-range DMN connectivity and social functioning has been reported in healthy adults (Di Martino et al., 2009), as well as in ASD or schizophrenia (Monk et al., 2009; Yerys et al., 2015). In the 22q11DS population, one study also demonstrated an association between DMN dysconnectivity and social functioning (Schreiner et al., 2017). Indeed, Schreiner et al. (2017) demonstrated a relationship between decreased connectivity between the PCC and the ACC/frontal regions and social competences in individuals with 22q11DS. Contrary to our expectations, we did not find any significant association between DMN dysconnectivity during social perception and social functioning measures in 22q11DS. Nevertheless, as we used a non-direct measure of social functioning (parent-reported questionnaire), this finding should be interpreted carefully. Further studies examining this relationship are required. However, the results showed a significant association between the strength of ILP-PCC/precuneus connectivity and the severity of negative symptoms in 22q11DS individuals. This result suggests that DMN dysconnectivity during social perception could notwithstanding contributes to social deficits observed in the 22q11DS population and then influence the emergence of negative symptoms. Moreover, this result is consistent with literature that demonstrated an association between altered DMN connectivity and negative symptoms in schizophrenia (Krishnadas et al., 2014; Wang et al., 2015). Nevertheless, in view of the preliminary aspect of this study, results should be interpreted carefully and replication studies are required.

4.4. Potential explanations for DMN divergent connectivity

Several non-mutually exclusive reasons could help to explain the pattern of divergent connectivity discussed above. Although, these explanations remain speculative, some evidence from the 22q11DS literature tends to support them.

4.4.1. Lack of coherence between structural and functional connectivity

First, the observed FC pattern within the DMN could relate to disrupted structural connectivity between brain regions. Indeed, correlations between functional and structural connectivity of the DMN have been reported in healthy controls (Greicius et al., 2009; Horn et al., 2014; Khalsa et al., 2014; Supekar et al., 2010; van Oort et al., 2014). Previous findings from a 22q11DS mouse model have identified reduced neural synchrony between anatomically distant brain regions, suggesting disrupted long-range FC (Sigurdsson et al., 2010). Furthermore, reduced white matter integrity in long-range fiber tracts in DMN regions has been found in 22q11DS individuals, suggesting impaired structural connectivity within the DMN (Schreiner et al., 2017). More recently, one study conducted in 22q11DS individuals also highlighted coherence between structural and functional connectivity of the DMN (Padula et al., 2017). Thus, structural connectivity defects may contribute to the divergent DMN connectivity observed in participants with 22q11DS.

4.4.2. Disrupted excitatory/inhibitory balance

At a cellular level, a potential explanation for aberrant DMN connectivity could be related to a disrupted excitation/inhibition (E/I) balance. E/I balance is crucial for efficient information transmission (Salinas and Sejnowski, 2001) (Vogels and Abbott, 2009) and unbalanced E/I has been demonstrated to be involved in psychiatric disorders such as schizophrenia (Uhlhaas and Singer, 2010) and ASD (Dani et al., 2005; Mariani et al., 2015; Rubenstein and Merzenich, 2003). E/I balance relies on glutamate/GABA ratio inputs (Padula et al., 2015a, 2015b; Gao et al., 2017). According to postmortem studies, various abnormalities could lead to unbalanced E/I, in particular reductions in parvalbumin containing interneurons (Lewis et al., 2012). A decrease of parvalbumin interneurons has been reported in studies conducted in a 22q11DS mouse model (LgDel/+) (Meechan et al., 2015; Steullet et al., 2017). Thus, reduction of parvalbumin interneurons in the 22q11DS population may lead to unbalanced E/I and impact connectivity within large-scale networks such as the DMN.

4.5. Limitations

There are several limitations to the current study. First, our sample size appears relatively small. As a consequence, we potentially miss out on results due to a lack of statistical power. Secondly, we used a non-direct measure of social functioning, which could explain why no association between DMN connectivity and social functioning was found. Future studies should investigate this relationship by examining social functioning through a more ecological measure. DMN FC during additional socio-cognitive processes (e.g. theory of mind) should be examined in further studies. Indeed, a better understanding of the role of the DMN during various socio-cognitive processes is required in 22q11DS. Finally, given the heterogeneity of medication taken by participants with 22q11DS, only the presence or absence of medication was considered as a covariate. Thus a better understanding of potential antipsychotic impact on such results appears of crucial importance.

This study is the first attempt to examine DMN functional connectivity during a socio-cognitive process in the 22q11DS population. Consistent with previous findings in resting-state fMRI, we found abnormal DMN FC compared to healthy controls. Moreover, we highlighted an association between stronger DMN FC and negative symptom severity in 22q11DS individuals. Taken together, these findings suggest that (1) DMN divergent connectivity is a hallmark in this syndrome; (2) DMN dysconnectivity may have a predictive value on the 22q11DS phenotype. Future investigations aimed at clarifying the mechanisms underlying the observed abnormal functional connectivity are required.

Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Lydia Dubourg: Data curation, Formal analysis, Writing - review & editing, Validation. **Pascal Vrticka:** Formal analysis, Supervision, Writing - review & editing, Validation. **Virginie Pouillard:** Data curation, Writing - review & editing, Validation. **Stephan Eliez:** Data curation, Formal analysis, Supervision, Writing - review & editing, Validation. **Maude Schneider:** Data curation, Formal analysis, Supervision, Writing - review & editing, Validation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.07.004.

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