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Comparing the neural bases of self-referential processing in typically developing and 22q11.2 adolescents

Maude Schneider[a], Martin Debbané[a,b,*], AnnaLaura Lagioia[a], Roy Salomon[c], Arnaud d'Argembeau[d], Stephan Eliez[a,e]

[a] Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, 1 David Dufour, CP 50, 1211 Geneva 8, Switzerland
[b] Adolescence Clinical Psychology Research Unit, Faculty of Psychology, University of Geneva, 40 Pont d'Arve, 1205 Geneva, Switzerland
[c] Laboratory of Cognitive Neuroscience, Brain-Mind Institute, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland
[d] Department of Cognitive Sciences, University of Liège, 4000 Liège 1, Belgium
[e] Department of Genetic Medicine and Development, University of Geneva School of Medicine, Michel-Servet 1, 1206 Geneva, Switzerland

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ABSTRACT

The investigation of self-reflective processing during adolescence is relevant, as this period is characterized by deep reorganization of the self-concept. It may be the case that an atypical development of brain regions underlying self-reflective processing increases the risk for psychological disorders and impaired social functioning. In this study, we investigated the neural bases of self- and other-related processing in typically developing adolescents and youths with 22q11.2 deletion syndrome (22q11DS), a rare neurogenetic condition associated with difficulties in social interactions and increased risk for schizophrenia. The fMRI paradigm consisted in judging if a series of adjectives applied to the participant himself/herself (self), to his/her best friend or to a fictional character (Harry Potter). In control adolescents, we observed that self- and other-related processing elicited strong activation in cortical midline structures (CMS) when contrasted with a semantic baseline condition. 22q11DS exhibited hypoactivation in the CMS and the striatum during the processing of self-related information when compared to the control group. Finally, the hypoactivation in the anterior cingulate cortex was associated with the severity of prodromal positive symptoms of schizophrenia. The findings are discussed in a developmental framework and in light of their implication for the development of schizophrenia in this at-risk population.

1. Introduction

The ability to think abstractly about oneself and to create a self-concept is a fundamental feature of the human mind (Leary and Buttermore, 2003). During adolescence, the self-concept is prone to deep reorganization; more abstract and complex representations of self and others tend to emerge (Labouvie-Vief et al., 1995). However, these representations still differ from those observed in adults. Discrepancies between self and others tend to be minimized (Labouvie-Vief et al., 1995) and others' opinions have a stronger influence on the self-concept (Sebastian et al., 2008).

The cerebral networks underlying self and other representations have been investigated in adults using paradigms in which the participants judge if a series of adjectives applies to themselves and to another person. These studies highlight the involvement of anterior midline regions during self-referential processing (SRP),

* Corresponding author at: Adolescent Clinical Psychology Research Unit, Department of Psychology and Educational Sciences, University of Geneva, 40 Boulevard du Pont d'Arve, 1211 Genève 4, Switzerland.
Tel.: +41 22 379 94 18; fax: +41 22 379 93 59.
E-mail address: martin.debbane@unige.ch (M. Debbané).

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particularly the anterior cingulate cortex (ACC; Modinos et al., 2009; Ochsner et al., 2005; Pfeifer et al., 2007; Ruby et al., 2009) and the medial prefrontal cortex (MPFC; Johnson et al., 2002; Lombardo et al., 2010; Modinos et al., 2009; Ruby et al., 2009). Posterior midline regions such as the posterior cingulate cortex (PCC) and the precuneus are also part of the self-network (Johnson et al., 2002; Lombardo et al., 2010; Ruby et al., 2009). However, Qin et al. (2012) observed that posterior regions are more specific to the processing of other-related information though they also display activity during SRP. Altogether, these studies suggest the presence of a significant overlap during self- and other-related processing, with ACC and ventral MPFC activation being the most specific to self. In addition, the extent to which self and other activations overlap could be influenced by the degree of familiarity or closeness to the other person. Two meta-analyses (Murray et al., in press; van der Meer et al., 2010) argue in favor of a ventro-dorsal gradient within medial frontal areas coding for self-relatedness, with ventral areas being dedicated to the processing of information regarding familiar others and dorsal areas coding for information regarding less-related others. In addition, Krienen et al. (2010) suggest that the ventral MPFC is particularly sensitive to the closeness of others (i.e. the social relevance of others to oneself).

In comparison, the neural underpinnings of SRP during adolescence have been explored only in a restricted number of studies. A few functional studies show that the MPFC is more activated in adolescents than in adults during the processing of self- (Pfeifer et al., 2009) and other-related information (theory of mind task; Sebastian et al., in press). Interestingly, Pfeifer et al. (2009) observed that adolescents also recruit cerebral regions implicated in social perception to a greater extent than adults during SRP, which suggests that adolescents automatically activate representations of what others think of them when processing self-relevant stimuli.

It is believed that self-disturbances underlie social functioning deficits and social cognitive difficulties (Nelson et al., 2009b). It may also be the case that an atypical development of brain regions dedicated to the processing of self-related information during adolescence increases the risk for psychopathological disorders later in life. Schizophrenia is a developmental disorder that is characterized by early dysfunctions of self-processing abilities (Nelson et al., 2009a). Indeed, self-monitoring difficulties (i.e. a tendency to falsely attribute self-generated thoughts and actions to an external agent) are thought to underlie the development of positive psychotic manifestations such as hallucinations and delusions (Frith, 1992). In the present article, we compared the neural correlates underlying self- and other-related processing in typically developing adolescents and young individuals with 22q11.2 deletion syndrome (22q11DS), a rare neurogenetic condition associated with increased risk for schizophrenia (Murphy, 2005). 22q11DS is the most common interstitial deletion in humans (Scambler, 2000) and is characterized by a 3Mb microdeletion in the majority of cases (Morrow et al., 1995). About 60 genes are contained within the deleted segment, some of which have been associated with specific characteristics of the 22q11DS phenotype such as cardiac or palate malformations (e.g. Scambler, 2000). Some candidate genes have also been identified for psychiatric dysfunction, mainly for impairments in social interaction (Vorstman et al., 2006) and psychosis (see Drew et al., 2011; Karayiorgou et al., 2010; Tunbridge et al., 2006). It is believed that 22q11DS is the third highest risk factors for schizophrenia spectrum disorders (Murphy, 2005) and accounts for up to 1–2% of cases of schizophrenia (Xu et al., 2008). Although major clinical features of schizophrenia in 22q11DS are identical to idiopathic forms of schizophrenia (Bassett and Chow, 2008), clinical studies suggest that 22q11DS is more often associated with early onset schizophrenia (Debbané et al., 2006; Gothelf et al., 1999). 30% of children and adolescents with 22q11DS display clinically relevant positive psychotic symptoms (Debbané et al., 2006) and up to 80% report at least one negative symptom of moderate to severe intensity (Schneider et al., in press). Furthermore, the prevalence of schizophrenia spectrum disorders and the severity of symptoms do not appear to differ significantly between men and women with 22q11DS, contrary to what is typically observed in the general population. Aside from the increased risk for schizophrenia spectrum disorders, 22q11DS is also characterized by an atypical brain development potentially contributing to the presence of atypical self-reflective processes. Firstly, several studies including 22q11DS children and adolescents observed structural brain abnormalities in midline areas (Bearden et al., 2009; Simon et al., 2005), especially within the ACC (Dufour et al., 2008; Schaer et al., 2010). Furthermore, several functional neuroimaging paradigms highlighted medial frontal hypoactivation in youths with 22q11DS (e.g. Kates et al., 2007; Reif et al., 2004).

To investigate brain networks underlying self- and other-related processing in these two adolescent populations, we designed an fMRI paradigm adapted from d'Argembeau et al. (2007), in which the adolescents had to perform judgments on adjectives describing personality traits in three conditions: self, best friend and fictional character (Harry Potter). As this task requires limited amount of working memory capacity and has already been used with children, it is ideally suited for 22q11DS adolescents whose cognitive profile is characterized by borderline intellectual functioning (Antshel et al., 2005; De Smedt et al., 2007; Green et al., 2009). The first aim of the present study was to characterize the specificities of SRP during adolescence and compare the obtained results to recent meta-analyses in adult populations. Specifically, since self-representations during adolescence are influenced by others' opinions (Sebastian et al., 2008), we hypothesized an overlap in the medial frontal region activation between the self and the best friend conditions. Furthermore, we expected to detect differences between the self and the Harry Potter condition mainly in the ventral MPFC, similar to what has been described in previous meta-analyses (Murray et al., in press; van der Meer et al., 2010). Additionally, in accordance with Qin et al. (2012), we expected to observe overlapping activations in medial posterior areas such as the PCC and the precuneus in all three conditions of interest. The second aim was to examine the integrity of networks sustaining self- and other-related

processing in 22q11DS adolescents. We hypothesized that they would display hypoactivation in medial frontal areas in comparison to typically developing adolescents, particularly during the self condition. Finally, we wanted to explore if group differences during the self condition were specifically associated with subthreshold positive symptoms of schizophrenia such as attenuated hallucinations or delusional ideas.

2. Material and methods

2.1. Participants

17 typically developing adolescents aged between 12 and 20 years old ($m = 15.79$, sd = 2.08; 5 females) and 14 participants with 22q11DS aged between 12 and 20 years old ($m_{age} = 16.13$, sd = 2.36, 7 females) were included in the study. The two groups did not significantly differ according to age ($t = 0.426$, $p = 0.673$) and gender ($\chi^2 = 1.372$, df = 1, $p = 0.242$). The 22q11.2 deletion was confirmed using DNA polymorphism analysis based on short sequence repeats or by fluorescence in situ hybridization performed on metaphase spreads spanning the deleted region. None of the participant had a current diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR criteria. However, some participants experienced subclinical psychotic manifestations such as auditory hallucinations ($N = 6$), visual hallucinations ($N = 2$), or delusional ideas ($N = 3$). 22q11DS participants were recruited through advertisements in patient association newsletters and by word of mouth. Typically developing adolescents were screened for the presence of any neurological problems, psychological or learning difficulties. They were recruited within the siblings of 22q11DS participants or from the Geneva state school system. Written informed consent was obtained from all participants and their parents under protocols approved by the Institutional Review Board of the Department of Psychiatry of the University of Geneva Medical School.

In addition to the fMRI paradigm described hereafter, all participants completed the Wechsler Intelligence Scale for Children (WISC-III-R; Wechsler, 1991) or adults (WAIS-III; Wechsler, 1997). Mean full-scale IQ was 74.57 (sd = 5.24) for 22q11DS adolescents and 107.81 (sd = 14.57) for typically developing adolescents. Finally, we used the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al., 2001; Miller et al., 2003) and the Positive And Negative Symptom Scale (PANSS; Kay et al., 1987) to assess psychotic manifestations in 22q11DS adolescents. We included two different scales in order to assess a wide range of psychotic symptoms, including subthreshold psychotic symptoms that are more specifically examined in the SIPS. In addition, the clinical manifestations included in the two scales are not identical. For example, the SIPS assesses "disorganized communication", which is not the case in the PANSS. Finally, the PANSS enables to compute *t*-scores based on the sum of all positive items whereas only raw scores are available in the SIPS. The SIPS evaluates 5 positive and 6 negative prodromal symptoms on a 7-point severity scale (ranging from 0 to 6); the severity score for positive symptoms was 3.5 on average (sd = 3.5) and 10.71 (sd = 4.05) for negative symptoms. The PANSS evaluates 7 positive symptoms and 7 negative symptoms on a 7-point severity scale (ranging from 1 to 7). Mean positive *t*-score was 34.57 (sd = 3.84) and mean negative *t*-score was 44.5 (sd = 7.23). All clinical evaluations were performed by a trained child psychiatrist (S.E.).

2.2. Design and procedure

We used a paradigm adapted from d'Argembeau et al. (2007) to evaluate self- and other-related processing in adolescents. Before the beginning of the experiment, all participants were asked to identify their best friend whose name was later used during the fMRI task. We also made sure that all participants had a sufficient knowledge on Harry Potter (meaning that they had at least read one book or watched one movie), which was used as the public figure during the task. Finally, participants were briefly trained outside the MRI to familiarize them with the experiment.

During the block design scanning session, the participants had to judge 40 adjectives describing personality traits in four conditions: does the adjective apply to themselves (SELF; e.g. "Are you brave?"), to their best friend (FRIEND; e.g. "Is Vincent brave?"), or to Harry Potter (HP; e.g. "Is Harry Potter brave?"). In the last condition, they had to evaluate the valence of the adjectives (e.g. "Is brave a positive adjective?"), which was used as a semantic baseline condition (SEM). They were asked to answer by pressing one of the two buttons of an MRI compatible button box (1 = yes; 2 = no). The scanning session involved 40 blocks equally divided into the 4 conditions. Each block contained an instruction screen lasting 3 s to inform about the judgment target and four trials during 3.5 s each. Two positive and two negative adjectives were present in every block. A black screen appeared between each trial during 1 s. The blocks were separated by a variable inter-block interval of 4–8 s (REST). A total time of approximately 18 min was dedicated to the task.

2.3. fMRI data acquisition

Functional images were acquired on a 3 T Siemens TIM Trio system [repetition time (TR) = 2400 ms, echo time (TE) = 30 ms, slice thickness = 3.20 mm, flip angle = 85°, FOV = 235 mm]. The functional scan session consisted of 455 volumes that comprised 38 slices oriented parallel to the AC-PC lines and collected in a descending sequence. The stimuli were presented on a screen placed in the back of the MRI that the participants saw through a mirror mounted on the head coil. In addition, high-resolution three-dimension anatomical images were obtained [TR = 2500 ms, TE = 30 ms, slice thickness = 1.1 mm, flip angle = 8°, 192 volumes, FOV = 220 mm].

2.4. fMRI data analysis

Data were processed and analyzed using Statistical Parametric Mapping 8 (SPM8; 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 excluded from the analyses. We then applied a slice-time correction to account for differences in slice acquisition times. Each participant's structural image was coregistered to the mean of the realigned functional images and segmented to obtain tissue classification. Finally, we normalized all functional images into the Montreal Neurological Institute template (MNI) using a 3-mm cubic voxel size and spatially smoothed them with an 8-mm isotropic Gaussian Kernel FWHM.

For each participant, brain responses were estimated at each voxel using a general linear model with block regressors. These block regressors examined brain activity for the SEM, SELF, FRIEND, and HP conditions. For each condition, 18-s blocks were defined, meaning that they began at the appearance of the first adjective and lasted until the disappearance of the fourth adjective. As for REST periods, they were treated as an implicit baseline condition. Realignment parameters were also included within the model to account for any residual motion. A high pass filter of 1/128 Hz was used to remove low frequency noise, and serial correlations were accounted for using an autoregressive AR (1) + white noise model. 20 contrasts maps were obtained for each individual and entered into the second-level analysis. We performed group comparisons using two-sample *t*-tests and within group comparisons using one-sample *t*-tests. The comparison between adolescents with mild mental retardation and typically developing individuals confront us to a statistical paradox: while one may be interested in covarying out IQ across groups, doing so moves much of the group-related variance to that covariated factor and is considered as statistically incorrect by a number of authors (e.g. Miller and Chapman, 2001). However, standard practice in fMRI studies examining group differences usually include covarying for variables even if they yield significant group differences. In order to give the reader the best understanding possible of these analyses, we decided to report below both types of group comparisons (not covaried and covaried for full-scale IQ score).

We generated SPM{T} maps with a threshold of $p < 0.001$. If not otherwise specified, statistical inferences were performed at the cluster level at $p < 0.05$ using Family-Wise correction for multiple comparisons across the entire brain volume. The peak locations of local maxima cluster of contiguous voxels were localized on a mean structural scan with approximate Brodmann areas estimated from Talairach and Tournoux (1988) atlas after having adjusted coordinates to allow for differences between the MNI and Talairach templates (http://www.bioimagesuite.org/Mni2Tal/index.html).

In order to explore the association between group differences and clinical variables, we performed region of interest (ROI) analyses using Marsbar (http://marsbar.sourceforge.net). The ROIs were defined around the peak of activation observed in a given contrast. A 6 mm radius sphere was built around the center of mass for each subject to extract the ROI value.

Table 1
Group difference in response times in each condition.

	Typical controls	22q11DS
RT self	1661.91 (221.83)	1608.93 (205.48)
RT friend	1653.88 (275.87)	1547.21 (281.25)
RT Harry Potter	1737.26 (272.28)	1622.43 (230.24)
RT semantic	1577.99 (247.24)	1593.08 (226.07)

3. Results

3.1. Behavioral results

Differences regarding response times between the two groups and the four different conditions were analyzed using a mixed design ANOVA 2 (diagnosis) × 4 (conditions) (see Table 1). This yielded a non significant effect of diagnosis ($F(1,29) = 0.622$, $p = 0.44$), a significant effect of conditions ($F(3,87) = 4.335$, $p = 0.007$) and a non significant interaction between diagnosis and conditions ($F(3,87) = 2.216$, $p = 0.092$). Post hoc Tukey indicated that typically developing adolescents answered significantly faster during the semantic baseline condition than during the Harry Potter condition ($p = 0.046$). There was no significant difference between the four conditions in the group of 22q11DS adolescents.

3.2. Neuroimaging results

3.2.1. Typically developing adolescents

3.2.1.1. Judgment targets vs semantic baseline. Brain regions activated in the self condition (SELF > SEM) were located within the perigenual ACC and the adjacent medial prefrontal cortex (2207 voxels, $p < 0.001$). A second cluster (178 voxels, $p = 0.001$) was located in the PCC. Brain regions activated in the close other condition (FRIEND > SEM) included the ACC and the medial frontal cortex (1339 voxels, $p < 0.001$), as well as the PCC and the cerebellum (527 voxels, $p < 0.001$). Finally, brain regions activated in the public figure condition (HP > SEM) were more largely distributed across the brain, with clusters encompassing the PCC (563 voxels, $p < 0.001$), the middle temporal gyrus and the precuneus (86 voxels, $p = 0.032$), the medial frontal gyrus (547 voxels, $p < 0.001$), the right superior temporal gyrus (BA 21: 101 voxels, $p = 0.018$ and BA38: 93 voxels, $p = 0.024$), and the left inferior and middle temporal gyri (141 voxels, $p = 0.004$) (see Table 2 for coordinates and *t* values and Fig. 1).

3.2.1.2. Effect of judgment target. The comparison between the self and the Harry Potter condition (SELF > HP) yielded two significant clusters of activation located in the ACC and caudate (626 voxels, $p < 0.001$) and the precuneus (64 voxels, $p = 0.043$). The reversed contrast (HP > SELF) yielded a significant cluster of activation (73 voxels, $p = 0.027$) in the PCC. Finally, the contrast between the close other and the public figure conditions (FRIEND > HP) yielded a significant cluster of activation (132 voxels, $p = 0.004$) in the ACC and the caudate (see Table 2 for coordinates and *t* values). All the other comparisons between the three judgment targets yielded non-significant clusters of activation.

Table 2
Cerebral regions showing significant increase in typically developing adolescents. Coordinates are in MNI atlas space, and brain regions estimated from Talairach and Tournoux (1988) atlas after normalization (Talairach and Tournoux, 1988).

k	*t*	MNI (*x*,*y*,*z*)	Hemisphere	Region	BA
Self > Sem					
2207	6.42	−6 53 −2	L	ACC	32
	5.96	0 32 22	L	ACC	24
	5.91	−3 38 −2	L	ACC	24
178	4.79	−12 −52 22	L	Cingulate gyrus	31
	4.34	9 −49 22	R	PCC	30
	4.30	−3 −46 22	L	PCC	23
Friend > Sem					
1339	6.70	0 35 19	L	ACC	32
	6.48	−9 41 −14	L	Medial frontal gyrus	10
	5.94	6 56 19	R	Medial frontal gyrus	9
527	5.99	6 −52 22	R	PCC	23
	5.87	−6 −52 22	L	PCC	23
	4.52	−6 −40 −2	L	Cerebellum	–
HP > Sem					
563	8.14	−12 −52 19	L	PCC	31
	6.48	−3 −55 10	L	PCC	29
	6.17	12 −52 22	R	Cingulate gyrus	31
86	7.06	−48 −70 22	L	Middle temporal gyrus	39
	3.79	−39 −76 37	L	Precuneus	19
547	6.52	3 41 −14	R	Medial frontal gyrus	11
	5.70	0 32 −17	L	Medial frontal gyrus	25
	5.54	3 59 10	R	Medial frontal gyrus	10
101	6.18	60 −4 −17	R	Superior temporal gyrus	21
	5.42	51 −7 −17	R	Temporal sub-gyral	21
93	6.08	42 17 −29	R	Superior temporal gyrus	38
	5.84	36 5 −29	R	Superior temporal gyrus	38
141	5.49	−51 −10 −17	L	Temporal sub-gyral	21
	5.20	−60 −7 −20	L	Inferior temporal gyrus	21
	4.80	−60 −16 −11	L	Middle temporal gyrus	21
Self > HP					
626	6.26	0 35 4	L	ACC	24
	5.36	−15 47 1	L	ACC	32
	4.91	−12 17 4	L	Caudate	–
64	4.90	18 −58 40	R	Precuneus	31
Friend > HP					
132	5.75	0 35 16	L	ACC	24
	3.51	0 23 1	L	Caudate	–
HP > Self					
73	6.31	12 −46 7	R	PCC	29
	5.45	6 −52 10	R	PCC	29
	4.09	−9 −49 7	L	PCC	29
Self > Rest					
1230	9.63	−6 20 58	L	Superior frontal gyrus	6
	8.29	−12 53 34	L	Superior frontal gyrus	9
	7.04	−9 44 43	L	Medial frontal gyrus	8
352	8.31	−45 26 −8	L	Inferior frontal gyrus	47
	5.80	−39 26 −17	L	Inferior frontal gyrus	47
	5.68	−51 17 7	L	Precentral gyrus	44
249	6.70	48 −67 −29	R	Cerebellum	–
	6.69	24 −79 −32	R	Cerebellum	–
	6.14	6 −79 −26	R	Cerebellum	–
363	5.19	−21 8 13	L	Putamen	–
	4.73	−18 −19 22	L	Caudate	–
	4.41	−15 −13 16	L	Thalamus	–
118	4.98	18 17 10	R	Caudate	–
	4.65	18 8 22	R	Caudate	–
	4.04	9 −1 16	R	Caudate	–
Friend > Rest					
1138	8.40	−6 20 61	L	Superior frontal gyrus	6
	7.46	0 56 19	L	Medial frontal gyrus	9
	7.06	−9 53 31	L	Superior frontal gyrus	9
366	6.12	−45 26 −8	L	Inferior frontal gyrus	47
	8.89	−39 23 −17	L	Inferior frontal gyrus	47
	5.84	−63 −10 −20	L	Inferior temporal gyrus	21
127	5.81	18 14 13	R	Caudate	–
	5.01	24 8 −5	R	Putamen	–

Table 2 (*Continued*)

k	*t*	MNI (*x*,*y*,*z*)	Hemisphere	Region	BA
365	5.64	−21 2 −8	L	Putamen	–
	5.21	−15 11 16	L	Caudate	–
	5.10	−15 −7 22	L	Caudate	–
78	5.37	24 −82 −29	R	Cerebellum	–
	3.94	45 −67 −32	R	Cerebellum	–
	3.63	42 −76 −29	R	Cerebellum	–
HP > Rest					
396	6.89	−6 20 61	L	Superior frontal gyrus	6
	5.95	−9 32 52	L	Superior frontal gyrus	8
	5.50	−12 20 49	L	Cingulate gyrus	32
125	4.27	−42 29 −8	L	Inferior frontal gyrus	47
	4.20	−48 23 1	L	Inferior frontal gyrus	45
	3.98	−39 38 −8	L	Middle frontal gyrus	47

Self = self condition; Friend = best friend condition; HP = Harry Potter condition; Sem = semantic baseline condition.

3.2.1.3. Judgment targets vs rest. In order to have a more direct comparison with studies using rest as baseline condition (e.g. Pfeifer et al., 2007, 2009), we also compared the three conditions of interest (self, best friend and Harry Potter) over rest, which was modeled as an implicit baseline condition. The contrast between the self condition and rest (SELF > REST) yielded significant clusters of activation located in the left superior frontal gyrus (1230 voxels, $p < 0.001$), the left inferior frontal gyrus (352 voxels, $p < 0.001$), the cerebellum (249 voxels, p 0.001), the left thalamus and basal ganglia bilaterally (363 voxels, $p < 0.001$; 118 voxels, $p = 0.011$). Brain regions activated in the close other condition (FRIEND > REST) were located in the left superior and medial frontal gyri (1138 voxels, $p < 0.001$), the left inferior frontal and temporal gyri (366 voxels, $p < 0.001$), the basal ganglia bilaterally (127 voxels, $p = 0.006$; 365 voxels, $p < 0.001$), and the right cerebellum (78 voxels, $p = 0.38$). Finally, the contrast between the public figure condition and rest (HP > REST) yielded clusters of activation encompassing the left superior frontal gyrus (396 voxels, $p < 0.001$), and the left inferior and middle temporal gyri gyrus (125 voxels, $p = 0.010$) (see Table 2 for coordinates and *t* values and Fig. 2).

3.2.2. 22q11DS adolescents

3.2.2.1. Judgment targets vs semantic baseline. No significant activation was observed when contrasting the three judgment targets (SELF, FRIEND and HP) against the semantic baseline condition (SEM).

3.2.2.2. Effect of judgment target. The comparison between self judgments and judgments concerning Harry Potter (SELF > HP) revealed a significant cluster of activation (170 voxels, $p < 0.001$) encompassing the lingual gyrus bilaterally, and the left cerebellum. The contrast between the public figure and the close other conditions (HP > FRIEND) yielded a significant cluster of activation in the right insula and caudate (70 voxels, $p = 0.048$) (see Table 3 for coordinates and *t* values). All the other comparisons between the three judgment targets yielded non-significant clusters of activation.

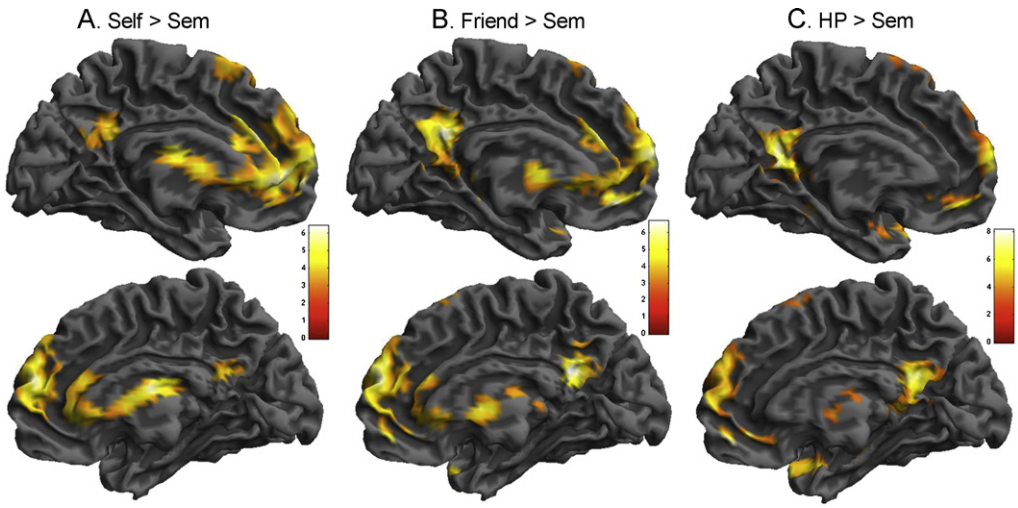

Fig. 1. Activations during the self condition > semantic baseline (A), the best friend condition > semantic baseline (B) and the Harry Potter condition > semantic baseline (C) in typically developing adolescents.

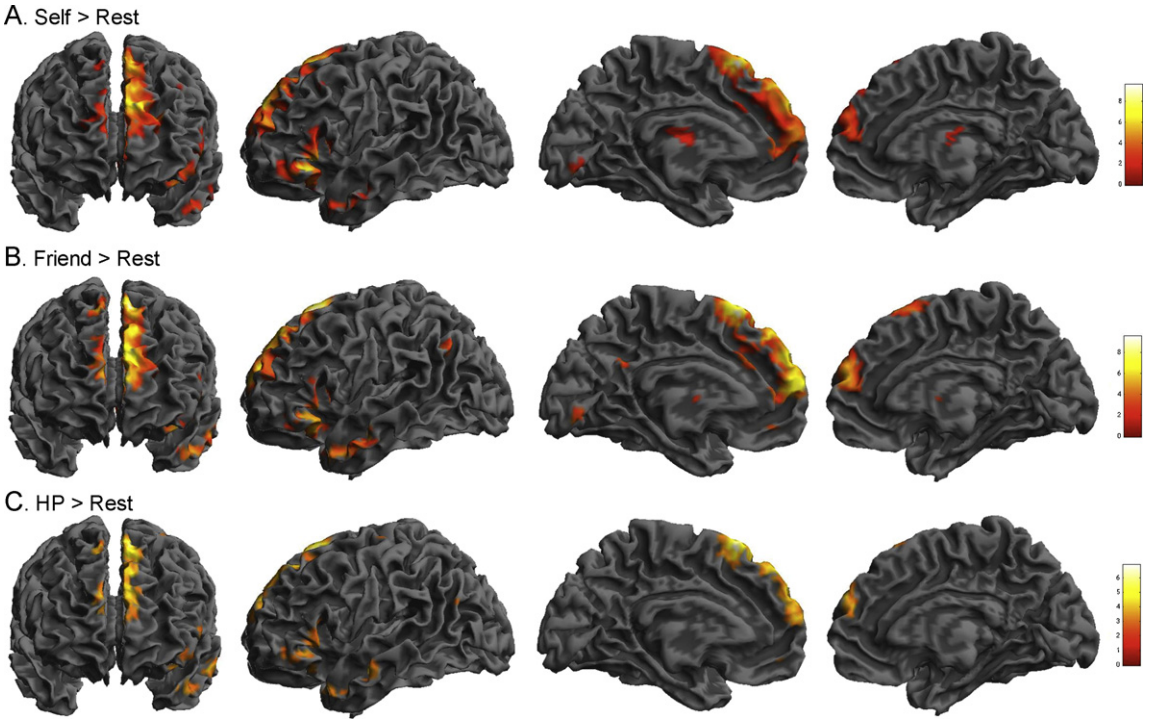

Fig. 2. Activations during the self condition > rest (A), the best friend condition > rest (B) and the Harry Potter condition > rest (C) in typically developing adolescents.

3.2.2.3. Judgment targets vs rest. In accordance to the analyses performed in typically developing adolescents, we also contrasted our three main conditions of interest against rest in 22q11DS youths. The contrast between the self condition and rest (SELF > REST) yielded significant clusters of activation within the left superior frontal gyrus (255 voxels, $p < 0.001$), the left inferior and middle temporal gyri as well as the fusiform gyrus (206 voxels, $p = 0.001$), the left inferior frontal gyrus (111 voxels, $p = 0.014$), and the left putamen and caudate (180 voxels, $p = 0.001$). The contrast between the close other condition and rest (FRIEND > REST) yielded clusters of activation in the left inferior and middle temporal gyri (99 voxels, $p = 0.016$), the putamen and caudate bilaterally (225 voxels, $p < 0.001$; 118 voxels, $p = 0.008$), the left inferior and middle frontal gyri (149 voxels, $p = 0.003$), the left superior frontal gyrus (265 voxels, $p < 0.001$), and the left precentral gyrus (79 voxels, $p = 0.036$) (see Table 3 for coordinates and t values and Fig. 3). The contrast between the public figure condition and rest (HP > REST) yielded no significant cluster of activation.

3.2.3. Group comparisons

Group comparisons revealed significant differences in the brain regions underlying self-related processing. The contrast between the self condition and rest (SELF > REST) yielded a significant cluster of activation (113 voxels, $p = 0.013$) encompassing the left caudate, the left ACC and the left superior frontal gyrus, which was significantly more activated in typically developing adolescents (see Fig. 4). We also observed significant group differences when contrasting the self condition over the semantic baseline (SELF > SEM) in the left caudate and the bilateral ACC (580 voxels, $p < 0.001$) using a threshold of $p < 0.005$. Finally, the group comparison for the SELF > HP contrast yielded a significant cluster of activation in the left ACC, the left medial frontal gyrus, and the right caudate (224 voxels, $p = 0.010$) using a threshold of $p < 0.005$ (see Table 4 for coordinates and t values). All the other group comparisons yielded non-significant clusters of activation.

Group comparisons covariating for full-scale IQ indicated that the cingulate cortex (69 voxels, $p = 0.044$) was significantly more activated in typically developing adolescents than 22q11DS participants in the SELF > SEM (IQ cov) contrast (see Table 4 for coordinates and t values). No significant group difference was observed when covarying out IQ in the SELF > REST and the SELF > HP contrasts.

3.2.4. ROI analyses

We performed ROI analyses localized around the first and second peaks of activation observed in the group comparison for the SELF > REST contrast (MNI coordinates: $x = -18$, $y = 23$, $z = 19$ (caudate nucleus) and $x = -18$, $y = 32$, $z = 16$ (ACC)) and the SELF > SEM contrast (MNI coordinates: $x = -3$, $y = 23$, $z = 4$ (caudate nucleus) and $x = -15$, $y = 44$, $z = -8$ (ACC)). Partial Pearson correlations controlling for full-scale IQ indicated that the extracted ROI values for the second peak of activation in the SELF > REST contrast were significantly associated with the PANSS positive t score ($r = -0.563$, $p = 0.045$) and marginally associated with the SIPS positive score ($r = -0.538$, $p = 0.058$). The values extracted from the other ROI analyses were not significantly associated with psychotic symptoms (all $p > 0.05$).

Table 3
Cerebral regions showing significant increase in adolescents with 22q11DS. Coordinates are in MNI atlas space, and brain regions estimated from Talairach and Tournoux (1988) atlas after normalization (Talairach and Tournoux, 1988).

k	*t*	MNI (*x*,*y*,*z*)	Hemisphere	Region	BA
Self > HP					
170	6.05	−3 −58 −2	L	Cerebellum	–
	4.95	15 −73 1	R	Lingual gyrus	18
	4.77	−9 −79 1	L	Lingual gyrus	18
HP > Friend					
70	5.36	36 5 16	R	Insula	13
	4.00	21 14 19	R	Caudate	–
	3.83	33 26 13	R	Insula	13
Self > Rest					
255	6.77	−9 44 43	L	Medial frontal gyrus	8
	6.26	−9 23 58	L	Superior frontal gyrus	6
	4.85	−15 53 34	L	Superior frontal gyrus	9
206	5.66	−63 −10 −23	L	Inferior temporal gyrus	21
	5.05	−45 −1 −29	L	Fusiform gyrus	20
	4.90	−60 −31 −14	L	Middle temporal gyrus	21
111	5.55	−42 26 −17	L	Inferior frontal gyrus	47
	5.40	−48 32 −11	L	Inferior frontal gyrus	47
	5.26	−48 23 −8	L	Inferior frontal gyrus	47
180	4.88	−27 2 −5	L	Putamen	–
	4.84	−21 −1 4	L	Putamen	–
	4.41	−12 11 10	L	Caudate	–
Friend > Rest					
99	7.21	−63 −13 −23	L	Inferior temporal gyrus	20
	4.34	−60 −28 −17	L	Middle temporal gyrus	21
	4.24	−51 −22 −20	L	Inferior temporal gyrus	20
225	6.28	−24 2 −5	L	Putamen	–
	5.07	−15 5 19	L	Caudate	–
	4.84	−12 14 7	L	Caudate	–
149	6.20	−42 35 −14	L	Inferior frontal gyrus	47
	5.52	−42 26 −17	L	Inferior frontal gyrus	47
	4.74	−48 41 −11	L	Middle frontal gyrus	47
265	5.78	0 53 19	L	Medial frontal gyrus	9
	5.18	−15 47 43	L	Superior frontal gyrus	8
	4.64	−12 26 58	L	Superior frontal gyrus	6
118	5.38	15 17 4	R	Caudate	–
	4.90	21 8 −5	R	Putamen	–
79	5.36	−39 −19 61	L	Precentral gyrus	4
	5.02	−33 −13 64	L	Precentral gyrus	6

Self = self condition; Friend = best friend condition; HP = Harry Potter condition.

Table 4
Increased activations in typically developing adolescents when compared to 22q11DS youth during the self condition. The Self > Rest and the Self > Sem (IQ cov) contrasts are thresholded at $p < 0.001$; the Self > Sem and the Self >HP contrasts are thresholded at $p < 0.005$.

k	*t*	MNI (*x*,*y*,*z*)	Hemisphere	Region	BA
Self > Rest					
113	5.34	−18 23 19	L	Caudate	–
	4.74	−18 32 16	L	ACC	32
	4.66	−27 47 25	L	Superior frontal gyrus	10
Self > Sem					
580	5.12	−3 23 4	L	Caudate	–
	4.23	−15 44 −8	L	ACC	32
	4.17	9 23 16	R	ACC	33
Self > HP					
224	4.80	−21 35 10	L	ACC	32
	4.27	−18 50 4	L	Medial frontal gyrus	10
	3.73	18 8 25	R	Caudate	–
Self > Sem (IQ cov)					
69	4.64	3 −1 31	R	Cingulate gyrus	24
	4.11	9 83 1	R	Cingulate gyrus	24

Self = self condition; Sem = semantic baseline condition; HP = Harry Potter condition; Self > Sem (IQ cov) = contrast between the self and the semantic baseline condition using full-scale IQ as a covariate.

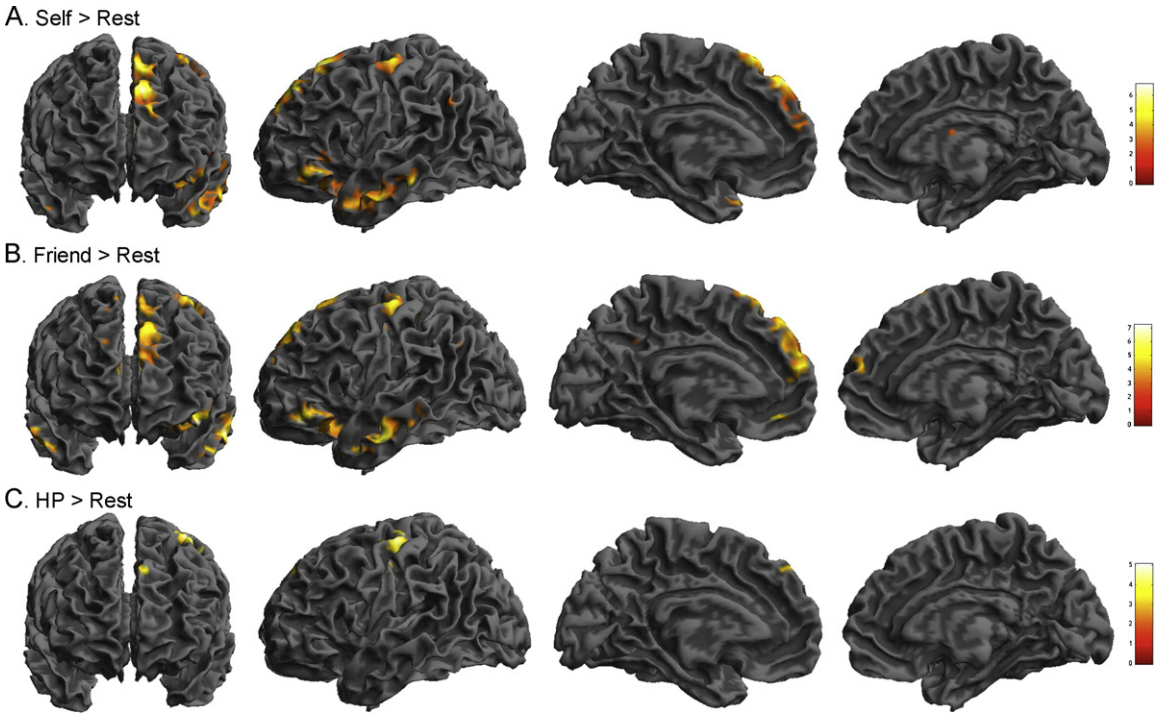

Fig. 3. Activations during the self condition > rest (A), the best friend condition > rest (B) and the Harry Potter condition > rest (C) in adolescents with 22q11DS.

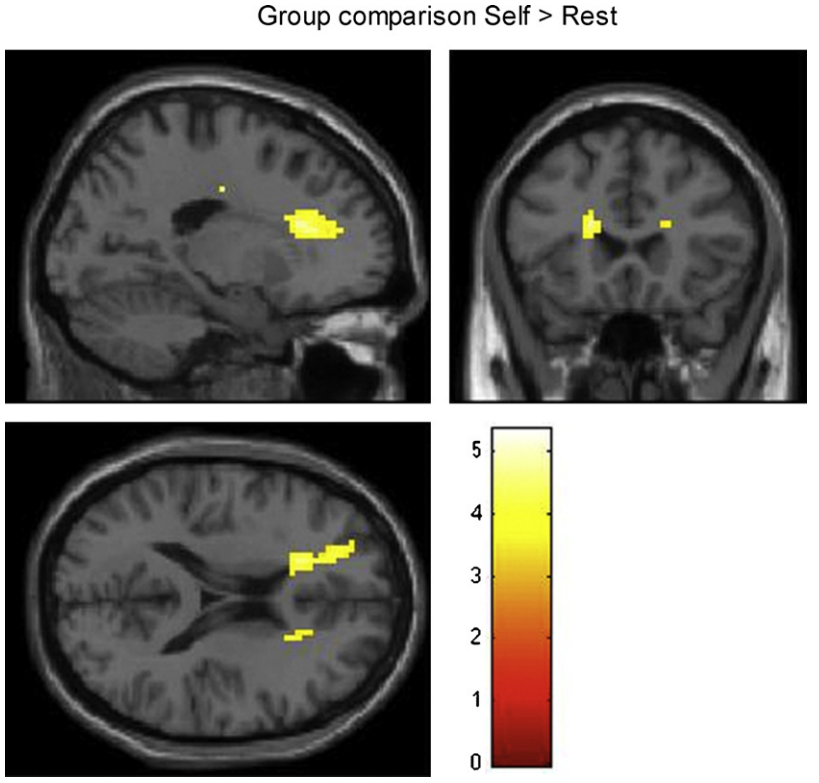

Fig. 4. Increased activations in typically developing adolescents compared to 22q11DS youths during the contrast self condition > rest.

We also performed a ROI analysis localized around the peak of activation observed in the group comparison for the SELF > SEM (IQ cov) contrast (MNI coordinates: $x = 3$, $y = -1$, $z = 31$ (cingulate cortex)). The ROI values were not significantly associated with positive psychotic symptoms (all $p > 0.05$).

4. Discussion

This study is the first to compare the neural bases of self- and other-related processing in typically developing adolescents and youths with 22q11DS, a rare neurogenetic condition associated with increased risk for schizophrenia (Murphy, 2005). We will first discuss the results obtained in our sample of typically developing adolescents and compare them with existing literature in children (Pfeifer et al., 2007, 2009) and adults (e.g. Murray et al., in press; Northoff et al., 2006; Qin et al., 2012; van der Meer et al., 2010). We will interpret the results in considering the self in a developmental framework. We will then discuss the results obtained in 22q11DS adolescents in light of their increased risk for psychosis and their characteristic behavioral and psychological phenotype.

4.1. Neural basis of self- and other-related processing during adolescence

In our sample of typically developing adolescents, the comparison between the semantic baseline and the three judgment targets revealed that the perigenual ACC was significantly more activated during the self and the close other conditions than the public figure condition. On the contrary, the PCC was significantly more activated during the public figure condition than the self condition. When contrasted over rest, the three judgment targets elicited a cluster of activation in the medial and lateral sides of the superior frontal gyrus. The direct comparison between the self and the best friend conditions did not yield a significant difference.

The present findings regarding self- and other-related processing during adolescence are consistent with the extensive literature in adult populations that attribute a central role to medial frontal areas in the processing of self-related information (e.g. Northoff et al., 2006). Indeed, our results indicate that the perigenual ACC is one of the few regions that was significantly more activated during self-reflected processing than during semantic processing or the processing of information regarding a public figure. This is also in line with the results of Pfeifer et al. (2007) that observed a greater involvement of the ACC and the adjacent VMPFC during self- than during social-knowledge retrieval in children. Furthermore and in accordance with our first hypothesis, these regions were equally activated during the self and the best friend conditions. This indicates that thinking about oneself and one's best friend during adolescence activates highly overlapping networks. In general, close others tend to be included in the self (Aron et al., 2004) and this might even be more the case in adolescents. Indeed, there is evidence that familiarity, similarity, and relatedness are all experienced as much more salient in adolescents' friendship. For example, Shulman et al. (1997) reported that tolerance for differing opinions within a friendship dyad increases between early and late adolescence.

On the contrary, the ACC and the VMPFC were not significantly activated during the self condition when contrasted over rest. This is consistent with fact that the default mode network (DMN) and self-related processing share common neural activation in these areas during adulthood (Qin and Northoff, 2011). Nevertheless, Pfeifer et al. (2007) did observe a significant activation in the ACC and VMPFC during self-retrieval when compared to rest in children. In their article, Pfeifer et al. (2007) suggested that children display a different pattern of brain activity in medial frontal areas during rest. According to this explanation, resting state activity would therefore exhibit strong developmental changes from childhood to adulthood particularly in medial frontal areas, which is consistent with several findings in the literature (for a review, see Uddin et al., 2010). For example, Kelly et al. (2009) observed that functional cingulate-based functional connectivity networks exhibit deep reorganization between childhood and adulthood and that adolescents display an intermediate pattern of connectivity. In particular, the authors highlighted that resting state networks that evolve the most during adolescence are associated with higher order cognitive functions and based in the perigenual ACC and VMPFC.

Aside from the ACC and the VMPFC, the contrast between the three judgment targets (self, best friend and Harry Potter) and rest yielded a significant cluster of activation in the dorsomedial prefrontal cortex. This is consistent with the previous result of Pfeifer et al. (2007), who also observed significant activation in the dorsomedial prefrontal cortex during self- and social knowledge retrieval in children. According to Pfeifer et al. (2007), since the dorsomedial prefrontal cortex has been associated with the processing of externally generated social information, it is possible that children and adolescents also rely on this kind of information to obtain a representation of themselves. In particular, psychological studies in the field of self-representation suggest that reflected self-appraisals—i.e. what others think of one person—have a greater influence on the self-concept during adolescence than adulthood (see Pfeifer et al., 2009).

In the present study, the PCC was significantly more activated during the processing of information regarding a public figure than self-related processing. The PCC is densely connected to the hippocampus and has been associated with autobiographical memory retrieval (Svoboda et al., 2006). Klein's work (Klein and Gangi, 2010; Klein and Lax, 2010; Klein et al., 2008), based on the observation of patients with neuropsychological impairments and on cognitive research with college students, suggest that episodic autobiographical memories are not necessarily retrieved when judging if an adjective is self-referential. This kind of task may more rely on the semantic memory system that also stores information about the self. On the other hand, deciding if an adjective is congruent with someone else's personality might depend to a greater extent on the episodic memory system. This might explain why the PCC was more strongly activated during the processing of a public figure.

4.2. Medial frontal dysfunctions and risk for psychosis in 22q11DS

Contrary to typically developing adolescents, our sample of 22q11DS adolescents did not show any significant difference between the three conditions of interest (self, best friend and Harry Potter) and the semantic baseline condition. When contrasted against rest, we observed that the self and the close other conditions elicited significant clusters of activation in the superior frontal gyrus, the inferior frontal gyrus and the middle temporal gyrus. Group comparisons indicated that 22q11DS adolescents had a significantly lower level of activation in the caudate nucleus, the ACC, and the anterior prefrontal cortex during the self condition when contrasted over rest, the semantic baseline condition or the public figure condition. Finally, we observed a significant association linking reduced ACC activation during the self condition to the level of positive psychotic symptoms in 22q11DS adolescents.

The most striking result in the present article is the reduced activation within the CMS during the processing of self- related information. From a structural point of view, these regions are particularly affected in 22q11DS. Midline brain structures – such as the cingulate gyrus, the medial cerebellum, the caudate and the brainstem – are more severely affected than other brain regions, both in volume (Simon et al., 2005) and cortical thickness (Bearden et al., 2009). Abnormalities of the corpus callosum have also been observed (Machado et al., 2007). According to Bearden et al. (2009), this particularity of the 22q11DS brain morphology results from abnormal neural migration more severely affecting medial regions. As most of the deleted genes located within the 22q11.2 region are highly expressed in the brain (e.g. Maynard et al., 2003), it is likely that some of them at least partly account for these structual changes. One might assume that midline cortical alterations contribute to the hypoactivation in medial frontal areas observed both in the present study and in other fMRI investigations (Kates et al., 2007; Reif et al., 2004). Nevertheless, our results indicate that medial frontal hypoactivation was not globally observed across all conditions but was specific to the self condition. This is in accordance with our third hypothesis and may indicate difficulties in building accurate and differentiated representations of oneself. It has been suggested that self-disturbances contribute to the presence of social functioning deficits and impaired social cognitive skills (Nelson et al., 2009b). Interestingly, children and adolescents with 22q11DS display specific deficits in recognizing facial emotions (Campbell et al., 2011), in theory of mind (Campbell et al., 2011) and in perceiving humor (Polimeni et al., 2010). They also exhibit decreased social functioning in comparison with their siblings (Kiley-Brabeck and Sobin, 2006). Finally, social withdrawal is a clinically significant manifestation in 22q11DS adolescents and represents a frequent parental concern.

Another possible consequence of decreased medial frontal activation during the self condition is that the source of self-generated information is not clearly identified, which might lead to greater confusions between self- and other-generated information. Two behavioral studies by Debbané et al. (2008,2010) argue in favor of this hypothesis since they highlighted source monitoring difficulties in adolescents with 22q11DS, and particularly an increased tendency to attribute internally generated information to an external source. This cognitive dysfunction has been observed consistently across the whole psychosis continuum (e.g. Brébion et al., 2002; Laroi et al., 2004) and has been identified as a relevant mechanism leading to the development of positive psychotic symptoms (Frith, 1992). In addition, the results of a recent neuroimaging study (Lagioia et al., 2011) suggest that medial frontal hypoactivation might underlie source monitoring difficulties and positive schizotypal traits during adolescence. Interestingly, our results further indicate that the severity of medial frontal hypoactivation during the self condition is significantly associated with positive psychotic symptoms in 22q11DS adolescents. It is therefore possible that hypoactivation of medial frontal areas during the processing of self-related information may contribute to source monitoring difficulties in 22q11DS, which contributes to the development of positive psychotic symptoms.

Group comparison also indicated that the caudate was significantly less activated in 22q11DS adolescents during the self condition. The caudate nucleus is part of the reward system and is also implicated in the processing of self-related information due to its dense connexions with medial frontal areas (Enzi et al., 2009). In addition, this structure has received great interest in the schizophrenia literature due to its high density of dopaminergic receptors and the putative role of dopaminergic dysfunction in the pathogenesis of positive symptoms (for a review, see Kapur, 2003; Kienast and Heinz, 2006). Kapur (2003) suggests that dysregulated dopamine transmission contributes to the development of psychotic symptoms through a process of aberrant salience attribution. It is therefore possible that abnormalities of the dopaminergic transmission in adolescents with 22q11DS contribute to caudate dysfunction during the processing of self-related information and to the emergence of positive psychotic symptoms.

In conclusion, the present study highlights the importance of investigating the neural correlates sustaining self and other representations during adolescence, a period during which the self-concept is highly evolving. Our study is the first to compare the processing of self- and other-related information in typically developing adolescents and youths with 22q11DS, a genetic condition associated with very high risk for schizophrenia. The present results suggest that adolescents with 22q11DS display reduced activation in medial frontal regions during the processing of self-related information. Furthermore, this atypical processing is associated to the early expression of positive psychotic symptoms. Longitudinal designs may further address how developmental interactions between self-related processing and symptom manifestations may promote clinical expressions of psychosis in older teenagers and young adults with 22q11DS. Decreased intellectual functioning in 22q11DS adds complexity to the association between atypical self-related processing and psychosis. Adolescents with mild intellectual impairments are known to more frequently report psychotic symptoms

(Johnstone et al., 2007); what the present results suggest is that for those affected by 22q11DS, atypical self-related processing is further associated with their vulnerability to experience early psychotic symptoms. While the question of self-processing in mental retardation is beyond the scope of this article, the present study indicates the relevance of employing simple cognitive paradigms such as the fMRI personality trait evaluation to uncover the neural underpinnings of self-processing in cognitively impaired adolescents. More research involving the larger array of neurogenetic disorders may further contribute to understanding the important comorbidity between cognitive impairment and psychiatric disorders. Psychosis and schizophrenia having often been described as "disorders of the self" (e.g. Lysaker and Lysaker, 2008), cognitive neuroscience research examining adolescent self-processing in relation to risk for psychosis is susceptible to shed new light on the neurodevelopmental markers of severe psychopathology.

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