



Morphological brain changes associated with negative symptoms in patients with 22q11.2 Deletion Syndrome



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ABSTRACT

Approximately 30% of individuals with 22q11.2 Deletion Syndrome (22q11DS) develop schizophrenia during adolescence/early adulthood, making this syndrome a model for the disorder. Furthermore, negative symptoms exist in up to 80% of patients diagnosed with 22q11DS. The present study aims to uncover morphological brain alterations associated with negative symptoms in a cohort of patients with 22q11DS who are at-risk for developing schizophrenia. A total of 71 patients with 22q11DS aged 12 to 35 (54% females) with no past or present diagnosis of a schizophrenia were included in the study. Psychotic symptom scores were used to divide patients into subgroups by means of a cluster analysis. Three major subgroups were evident: patients with low negative and positive symptoms; patients with high negative symptoms and low positive symptoms; and patients with high negative and positive symptoms. Cortical volume, thickness and gyrification were compared between subgroups using *FreeSurfer* software. Results showed that patients with high negative symptoms, compared to those with low negative symptoms, have decreased gyrification in the medial occipito-temporal (MOT) and lateral temporo-parietal (LTP) cortices of the left hemisphere, and in the medial temporal (MT)/posterior cingulate (PCC) cortices of the right hemisphere. These findings suggest that high negative symptoms are associated with gyrification reductions predominantly in medial occipital and temporal regions, which are areas implicated in social cognition and early visual processing. Furthermore, as cortical folding develops in utero and during the first years of life, reduced gyrification may represent an early biomarker predicting the development of negative symptoms.

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1. Introduction

22q11.2 Deletion Syndrome (22q11DS) is a neurogenetic condition with an occurrence rate of 1 in 1000–4000 live births (Grati et al., 2015; Oskarsdóttir et al., 2004). An estimated 30–40% of individuals with 22q11DS will develop schizophrenia (Murphy et al., 1999; Schneider et al., 2014a), making it an attractive model for studying the developmental patterns of schizophrenia and other psychotic disorders (Bassett and Chow, 1999; Gothelf et al., 2005; Murphy and Owen, 2001). Up to 50% of adolescents with 22q11DS report positive symptoms, while up to 80% present attenuated negative symptoms (Schneider et al., 2012; Stoddard et al., 2010). Thus, negative symptoms appear to be one of the clinical characteristic of 22q11DS since they are

present in roughly a third of patients in the absence of positive symptoms (Schneider et al., 2014b). Additionally, negative symptoms are more severe in patients with 22q11DS at risk for developing psychosis compared to at-risk subjects without the microdeletion (Armando et al., 2012; Tang et al., 2015).

We therefore argue that the study of negative symptoms is critical as they have a higher prevalence than positive symptoms in the prodromal psychotic phase (Cornblatt et al., 2003; McGlashan et al., 2001; Phillips et al., 2005; Schultze-Lutter et al., 2010). Negative symptoms are often accompanied by cognitive deficits (Addington et al., 1991; Basso et al., 1998), worse psychosis outcome (Milev et al., 2005), social impairments (Lincoln et al., 2011; Milev et al., 2005), and poorer occupational and daily functioning (Milev et al., 2005; Rabinowitz et al., 2012). Furthermore, negative symptoms are more persistent and difficult to treat than positive symptoms, as they are not remedied by current antipsychotics (Boonstra et al., 2012; Chang et al., 2011).

Different symptomatic profiles in patients with 22q11DS may be associated to differences in brain morphology. Indeed, studies conducted in non-syndromic schizophrenic patients have shown that alterations

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in connectivity (Oertel-Knöchel et al., 2014), cortical thickness (Oertel-Knöchel et al., 2013; Padmanabhan et al., 2015), and cortical volume (Padmanabhan et al., 2015) in temporal brain regions are related to high positive symptoms, while alterations in white matter volume (Sanfilipo et al., 2000), surface area (Padmanabhan et al., 2015), and cortical volume (Benoit et al., 2012; Koutsouleris et al., 2008; Sigmundsson et al., 2001) in frontal and temporal brain regions are related to high negative symptoms. A decrease in gyrfication throughout the entire brain has also been reported when comparing non-syndromic patients with schizophrenia to healthy participants (Sallet et al., 2003). Moreover, non-syndromic subjects at risk for developing schizophrenia also present morphological alterations, specifically changes in cortical volume in the temporal (Job et al., 2006, 2005) and prefrontal regions (Job et al., 2005, 2002) when compared to healthy controls. Most of the mentioned findings, however, did not investigate differences between subgroups of patients with distinct symptomatic profiles, but instead conducted post-hoc correlation analyses that may have only detected linear correlations between symptom scores and morphological measures. Nevertheless, recent studies have begun using more specific approaches involving the separation of patients with schizophrenia into subgroups based on their symptomatic profile. For example, extensive deficits in prefrontal cortical regions of schizophrenic patients with predominantly negative symptoms have been reported in comparison to those with mainly positive or disorganized symptoms (Nenadic et al., 2010; Zhang et al., 2015).

Brain alterations related to psychotic symptoms have also been reported in 22q11DS. For instance, altered cortical thickness in the orbitofrontal cortex (Jalbrzikowski et al., 2013), volumetric reductions in the temporal lobe (Kates et al., 2011), and reductions in overall gyrfication (Kunwar et al., 2012) have been related to positive symptoms in these patients. Cortical thickness reductions in left superior frontal gyrus and in the fusiform and lingual gyri have also been observed in patients with 22q11DS who have been diagnosed with schizophrenia compared to those who have not (Schaer et al., 2009). However, most of these findings refer mainly to positive symptoms.

In the present study, we aimed to gain insight into morphological brain differences associated with the manifestation of negative symptoms in patients with 22q11DS. At first, we conducted a cluster analysis on the psychotic symptom scores of 71 patients with 22q11DS in order to obtain subgroups of patients differing in symptomatic profiles. Then, we compared gray matter morphological measures (volume, thickness, and gyrfication) between these subgroups. We hypothesize that negative symptoms would be more prevalent than positive symptoms in our 22q11DS cohort as previously shown by other studies (Schneider et al., 2014b, 2012; Stoddard et al., 2010). We also expect to observe differences in cortical thickness, volume, and gyrfication between groups of patients with different symptomatic profiles.

2. Methods

2.1. Participants

The cross-sectional sample of patients with 22q11DS included in the analysis was collected in the context of a longitudinal study started in 2002 (Maeder et al., 2016; Schaer et al., 2009). Information regarding the selection of patients for this study, along with their demographic details, is reported in the Supplementary material. Patients were recruited through announcements and advertisements in the patient association newsletters and through word of mouth. Written informed consent was obtained from all participants or their parents, according to protocols approved by the Institutional Review Board of the Department of Psychiatry at the University of Geneva Medical School. The presence of the 22q11.2 microdeletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR).

The presence of a psychiatric diagnosis was assessed in these patients by an experienced psychiatrist (SE) using the Diagnostic

Interview for Children and Adolescents Revised (DICA-R), the psychosis supplement from the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Based on these assessments, we included in the study only patients with no past or present diagnosis of schizophrenia. Our final group included 71 patients with 22q11DS between the ages of 12 and 35 (mean age = 19.9 y.o., SD = 4.9, 33 (46%) males and 38 (54%) females). Patients below 12 years of age were excluded to minimize the number of false negatives (i.e. patients who are currently not symptomatic but who will develop symptoms later on) in accordance with previous studies (Gothelf et al., 2013). The mean IQ, as measured with the Wechsler Adult Intelligence Scale (WAIS-III) or the Wechsler Intelligence Scale for Children (WISC-III), was 70.6 (SD = 11.3).

2.2. Psychotic symptoms

The presence of positive and negative psychotic symptoms was assessed in each participant using the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Based on the results of a previously conducted factorial analysis, the SIPS and PANSS items were grouped into one positive categorical variable and two negative categorical variables (Decreased Motivation And Pleasure and Decreased Expression) (Schneider et al., 2014b, 2012). The three categorical variables were calculated as the mean of select PANSS and/or SIPS items as can be seen in Table 1.

2.2.1. Cluster analysis

A cluster analysis was conducted using the categorical variables mentioned in the previous paragraph with the aim of reproducing the results reported in Schneider et al., 2014b on an overlapping sample of patients (there are 23 patients in common between the actual and previous study). Briefly, hierarchical clustering was performed, followed by a K-means clustering method to confirm the outcome.

The mean age, IQ, and symptom severities were compared between the resulting subgroups using nonparametric Mann-Whitney *U* tests. Gender differences between the subgroups were assessed using a chi-square test. All analyses were conducted using the SPSS software version 22.

Table 1

PANSS and SIPS items used to calculate each of the three categorical variables, based on a previously conducted factorial analysis by Schneider et al. (2012).

Positive variable	Negative variable (Decreased Motivation and Pleasure)	Negative variable (Decreased Expression)
SIPS P1 Unusual Thought Content/Delusional Idea	SIPS N1 Social Anhedonia	SIPS N3 Expression of Emotion
SIPS P2 Suspiciousness	SIPS N2 Avolition	SIPS N4 Experience of Emotion and Self
SIPS P3 Grandiosity	SIPS D4 Personal Hygiene	PANSS N1 Blunted Effect
SIPS P4 Perceptual Abnormalities/Hallucinations	PANSS N3 Poor Rapport	PANSS N2 Emotional Withdrawal
SIPS P5 Disorganized Communication	PANSS N4 Passive Social Withdrawal	PANSS N5 Difficulty in Abstract thinking
SIPS D4 Personal Hygiene	PANSS G16 Active Social Avoidance	PANSS N6 Lack of Spontaneity/Flow of Conversation
		PANSS N7 Stereotyped Thinking
		PANSS G7 Motor Retardation

2.3. Imaging

2.3.1. Magnetic resonance images (MRIs) acquisition and processing

The T1-weighted MRIs were obtained for each patient at a maximum 1 day interval from the clinical assessment using a Siemens Trio 3 scanner at the Center for Biomedical Imaging (CIBM) in Geneva using a 3D volumetric pulse sequence with the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices.

Images were then processed using a semi-automated procedure with the *FreeSurfer* software version 5.1 (<https://surfer.nmr.mgh.harvard.edu/>). For more information on precise methods of image analysis done by this software, refer to Fischl et al. (2001). Briefly, the processing pipeline included intensity normalization, segmentation of gray and white matter, and removal of non-brain tissue (Dale et al., 1999; Fischl et al., 1999). Three-dimensional reconstructions of cortical surfaces were then obtained at the boundary between the white and gray matter (white surface), and at the boundary between the gray matter and cerebrospinal fluid (pial surface). All reconstructed surfaces were manually inspected and corrected.

Starting from the reconstructed surfaces, 3 morphological measures were computed using *FreeSurfer*: local cortical volume, cortical thickness, and the local gyrification index (IGI). Cortical thickness is defined as the distance between the pial and the white surface and is calculated by finding the shortest direct path between them (Fischl and Dale, 2000). The local gyrification index (IGI) is a vertex-wise measure elucidating gyral complexity and is computed according to the method described in (Schaer et al., 2008).

2.3.2. Statistical analyses

Vertex-wise statistical analyses were computed using a general linear model with the Query Design Estimate Contrast (QDEC) in *FreeSurfer*. First, cortical surfaces from each participant were registered to a study-specific average template. Thickness and volume values were then smoothed using a full width at a half maximum (FWHM) of 10 mm. As the IGI values are already smoothed because of the way they are computed (Schaer et al., 2008), a smoothing at a FWHM of 5 mm was used. Gender and age were added as covariates in the model. A Monte Carlo multiple comparisons correction was performed at a significance threshold of 0.05.

3. Results

3.1. Cluster analysis

The hierarchical cluster analysis produced 3 distinct subgroups of patients based on their psychotic symptom expression (Fig. 1). The same results were further confirmed by the k-means cluster analysis.

As shown in Table 2, the numbers of patients in each of the three subgroups were divided as follows: 31 patients in cluster 1, 6 in cluster 2, and 34 in cluster 3. Patients belonging to cluster 1 exhibited high negative symptom scores and low positive symptom scores and were labeled as 'HL - high negative/low positive'. Patients in cluster 2 exhibited high negative and positive symptom scores and were labeled as 'HH-high positive/high negative symptoms'. Finally, patients in cluster 3 presented low mean severities in all scores and were labeled as 'LL-low positive/low negative symptoms'.

As expected, the severity of positive symptoms was significantly higher in the HH group compared to both the HL ($p < 0.0001$) and the LL ($p < 0.0001$) groups, while it was not significantly different between the HL and the LL group ($p = 0.11$). The severity of negative symptoms for the dimension "decreased motivation and pleasure" was significantly higher in the HH group compared to the other two groups ($p < 0.0002$) and also in the HL group compared with the LL group ($p < 0.0001$). Finally, the severity of negative symptoms for the dimension "decreased expression" was significantly higher in the HH group

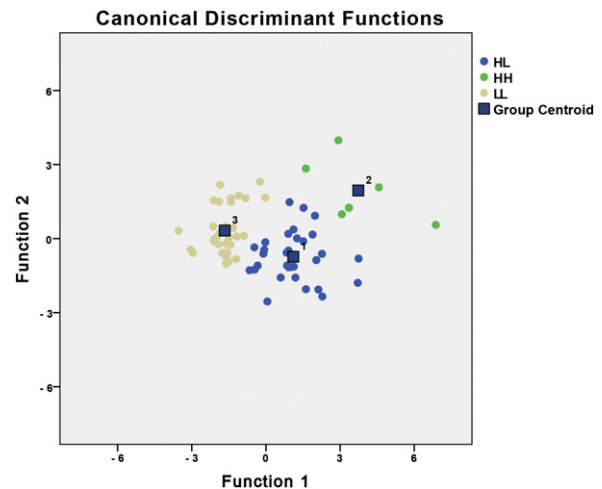


Fig. 1. The plot shows the 3 resulting subgroups from the hierarchical cluster analysis: low levels of symptoms (LL), high negative/low positive symptoms (HL), and high levels of symptoms (HH).

compared to the LL group and in the HL group compared to the LL group ($p < 0.0001$), but did not differ between the HH and HL groups ($p = 0.14$).

There were no significant differences in age (HH vs. HL $p = 0.56$, HH vs. LL $p = 0.59$ and HL vs. LL $p = 0.98$) or gender (HH vs. HL $p = 0.19$, HH vs. LL $p = 0.073$ and HL vs. LL $p = 0.46$) between the three subgroups. However, IQ significantly differed in the HL vs. LL ($p = 0.007$) and HH vs. LL ($p = 0.015$) comparisons, but not in HL vs. HH ($p = 0.385$).

3.2. Morphological analysis

Cortical thickness, volume, and gyrification were compared between the HL and LL subgroups. The HH subgroup was not included in the morphological analysis, as it comprised only 6 patients.

There were no significant group differences in cortical volume and thickness between the HL and LL subgroup. The local gyrification index (IGI), however, was decreased in patients within the HL subgroup compared to the LL subgroup in the following brain regions: the medial occipito-temporal (MOT) and the lateral temporo-parietal (LTP) cortices of the left hemisphere, and the medial temporal/posterior cingulate cortex (MT/PCC) of the right hemisphere (Fig. 2 and Table 3).

Since significant differences in IQ were observed between the HL and LL subgroups, we repeated the analysis using IQ as a covariate. The same results were evident after accounting for the effect of IQ.

3.3. Post-hoc correlation analyses

Post-hoc correlation analyses were conducted to determine if there were any correlations between negative subscale items and average IGI values in each affected brain regions. As can be seen in Fig. 3, significant correlations were found between the SIPS N1 subscale item, social anhedonia, and the MOT ($RHO = -0.5$; $p < 0.01$) and MT/PCC regions ($RHO = -0.4$; $p < 0.05$). These correlations indicate that decreased gyrification is associated to an increased severity of social anhedonia.

4. Discussion

This study represents the first attempt to better characterize brain morphological correlates of negative symptoms in patients with 22q11DS. Our results confirmed previous findings showing that negative symptoms are highly prevalent in patients with 22q11DS. Furthermore, we showed that patients with high negative symptoms have reduced cortical folding compared to patients with low symptom severities, in regions that encompass the medial occipital and temporal

Table 2
Demographic information.

Cluster	Group characteristic	N	Variable	Mean variable score	σ	Mean Age	Gender ratio	Mean IQ
1	High Negative, Low Positive (HL)	31	Positive	2.09	0.71	18.9	48% male 52% female	67.7
			Negative (Decreased Motivation and Pleasure)	3.43	0.64			
			Negative (Decreased Expression)	3.39	0.67			
2	High Negative, High Positive (HH)	6	Positive	4.44	0.60	21.6	83% male 17% female	63.2
			Negative (Decreased Motivation and Pleasure)	4.92	0.98			
			Negative (Decreased Expression)	4.08	1.13			
3	Low negative, Low positive (LL)	34	Positive	1.80	0.72	19.3	38% male 62% female	74.7
			Negative (Decreased Motivation and Pleasure)	1.98	0.39			
			Negative (Decreased Expression)	1.90	0.35			
Total	Total	71	Positive	2.15	1.00	19.3	46% male 54% female	70.6
			Negative (Decreased Motivation and Pleasure)	2.86	1.10			
			Negative (Decreased Expression)	2.73	1.01			

cortices. We further showed that altered gyrification in the above-mentioned brain regions was related to the severity of social anhedonia. In the following paragraphs, we will discuss our hypotheses and compare our results with the existing literature in patients with schizophrenia.

4.1. Patients with 22q11DS manifest pronounced negative symptoms

According to our first hypothesis, we found that negative symptoms are more prevalent than positive symptoms in 22q11DS, thus replicating previous results (Schneider et al., 2014b). Indeed, only a small percentage of patients with 22q11DS manifest high positive and negative symptoms (~10%), while around half of patients have minimal or absent symptoms. However, more interestingly, 30–40% of patients experience high negative symptoms only. Despite their high prevalence, negative symptoms are not yet well characterized in patients with 22q11DS, and the studies investigating the relationship between symptoms severities and psychotic symptoms often referred to positive symptoms only (Jalbrzikowski et al., 2013, Kates et al., 2011, Kunwar et al., 2012).

4.2. Morphological brain changes associated with negative symptoms in patients with 22q11DS

With the aim of better characterizing the morphological brain alterations associated to negative symptoms in 22q11DS we compared

cortical thickness, volume, and gyrification between patients with low levels of symptoms and patients with prevalent negative symptoms. We did not find a relationship between cortical thickness or volume and psychotic symptoms. However, we found that reduced gyrification in the medial occipito-temporal (MOT) and lateral temporo-parietal (LTP) regions of the left hemisphere, and in the medial temporal/posterior cingulate cortices (MT/PCC) in the right hemisphere was specifically related to negative symptoms.

Contrary to our results, previous studies conducted in non-syndromic schizophrenic patients have found associations between negative symptoms and altered cortical volume and thickness. For instance, decreased cortical volume has been observed in the medial and lateral temporal lobe (including the superior temporal gyrus), in the medial and lateral frontal lobe (including the anterior cingulate cortex, insula, and inferior frontal gyrus), and in limbic regions in schizophrenic patients with prevalent negative symptoms when compared to healthy controls (Benoit et al., 2012; Koutsouleris et al., 2008; Sigmundsson et al., 2001). Moreover, when comparing patients with schizophrenia with different types of psychotic symptoms, Nenadic et al., 2010 reported extensive prefrontal cortical deficits in those with higher negative symptoms compared to the ones with greater positive and disorganized symptoms. Similarly, Zhang et al. (2015) reported cortical volume alterations in the ventromedial prefrontal cortex and cerebellum in schizophrenic patients with predominantly negative

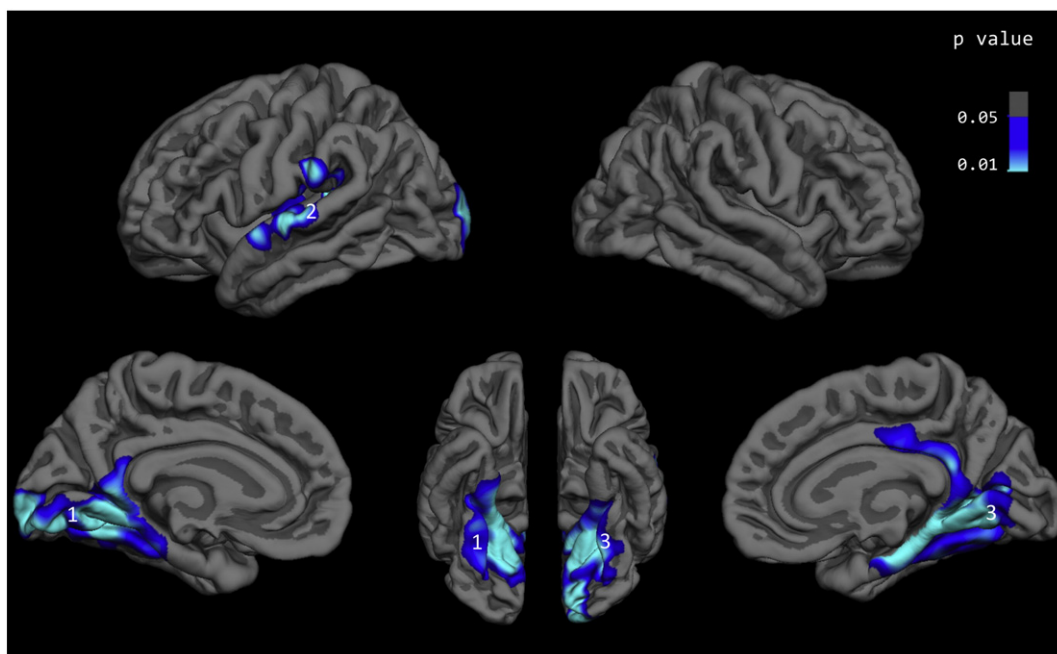


Fig. 2. Brain maps showing the regions of reduced gyrification in the HL subgroup compared to the LL subgroup. Gyrification was decreased in the medial occipito-temporal (MOT) and lateral temporo-parietal (LTP) cortices of the left hemisphere, and in the medial temporal/posterior cingulate (MT/PCC) cortices in the right hemisphere.

Table 3
Substructures included within each significant region along with peak co-ordinates and region size information.

Hemisphere	Peak region	Areas included in region	Peak co-ordinates (x, y, z Thalairach coordinates in mm)	Size of region (mm ²)	p-Value
Left	Medial occipito-temporal (MOT)	Fusiform, parahippocampal, (anterior) isthmus cingulate, lingual, lateral occipital, (anterior) pericalcarine.	TalX = -19.7 TalY = -54.2 TalZ = -2.9	6024	0.00010
Left	Lateral temporo-parietal (LTP)	Superior temporal, (inferior) supramarginal, insula, (anterior) transverse temporal.	TalX = -44.0 TalY = -31.6 TalZ = 5.1	3347	0.00060
Right	Medial temporal/posterior cingulate cortex (MT/PCC)	Fusiform, parahippocampal, lingual, isthmus cingulate, (medial) cuneus, posterior cingulate.	TalX = 20.0 TalY = -32.4 TalZ = -8.0	5486	0.00010

symptoms compared to those with mainly positive and disorganized symptoms.

The fact that we observed changes in gyrification but not in cortical thickness in our group of patients with 22q11DS may be explained by the varying neurodevelopmental spatiotemporal dynamics, such as differing initiation periods and growth rates, between these two measures (Boardman et al., 2006; Rajagopalan et al., 2011). In particular, postnatal cortical thickness growth rates considerably exceed those of gyrification during the first year of life (Li et al., 2015, 2014), while the gyrification process is typically completed in-utero and shortly after birth (Armstrong et al., 1995; Garel et al., 2003). Given the protracted development of cortical thickness, this measure is heavily related to age. Thus, the age range of the patients included in this study may have been too large to detect changes associated with negative symptoms. Also, as gyrification is established early in life, it may represent a strong biomarker that is already present from birth. However, further longitudinal studies will be required in order to confirm the presence of these alterations in gyrification before the development of negative symptoms.

4.3. Association between altered gyrification and social anhedonia in patients with 22q11DS with prevalent negative symptoms

We further found that decreased gyrification in the left MOT and right MT/PCC regions was associated with the inability to experience pleasure from social interactions (i.e. social anhedonia). The fusiform gyrus, which is included in the MOT and MT/PCC regions, is strongly implicated in face processing which is a crucial aspect of social cognition (Kanwisher et al., 1997; Kanwisher and Yovel, 2006; Tsao et al., 2008). This result is in line with studies showing that adolescents with 22q11DS who have higher levels of negative symptoms typically perform worse on facial recognition tasks (Schneider et al., 2015). Generally speaking, reduced gyrification in these areas may suggest that neurodevelopmental deficits in social processing, as well as in learning

and visual processing, are linked to the expression of negative symptoms.

4.4. Limitations and conclusion

This study comes with some limitations. First, though we were able to study negative symptoms independently, studying the effects of high negative symptoms in combination with high positive symptoms would also be of great importance. In this study, such analyses were not possible given the low number of patients expressing high positive and negative symptoms. Since the distribution of high levels of symptoms in a population of 22q11DS patients is expected to be around 11% (Schneider et al., 2014b), in order to gain a number of participants large enough to be included in the morphological analyses, a larger sample of patients will be required. Secondly, longitudinal analyses are needed in order to reveal cortical trajectories during development and how they relate to psychotic symptoms, thus allowing us to observe morphological differences before and after psychotic symptom development. This can potentially provide biomarkers indicating a possible development of psychosis, which could prove extremely useful for earlier interventions.

In conclusion, high negative symptom severity appears to be associated with reduced gyrification in patients with 22q11DS in regions related to social cognition, as well as in visual and language processing. Gyrification makes for a good neural biomarker candidate since it is established early in life. Gaining a better understanding of phenotypes associated with negative symptoms will be highly useful in the future understanding of the pathophysiology underlying negative symptomatology. The present study was the first step taken towards characterizing how differences in brain morphology relate to types and severities of psychotic symptoms in individuals with 22q11DS. Developing a clear understanding into the phenotypes associated with psychotic symptoms can unveil neural biomarkers predating the development of schizophrenia in patients both with, and potentially without, 22q11DS.

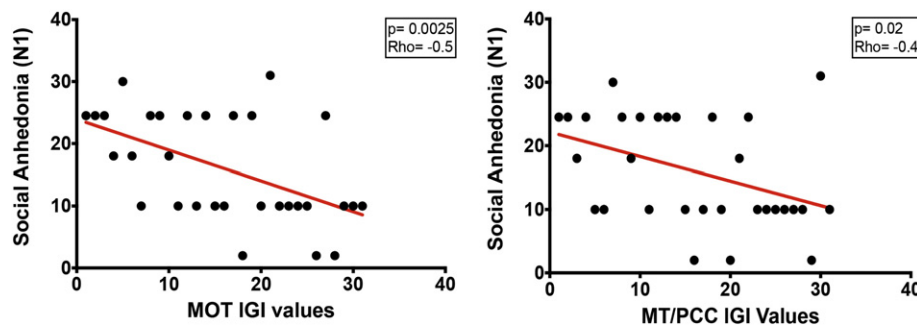


Fig. 3. Spearman's rank correlations between cortical gyrification and psychotic symptoms. A significant negative correlation was observed in the HL subgroup between the social anhedonia N1 SIPS subscale item and the IGI values in the left MOT and right MT/PCC regions. The plotted data are the ranks of the residuals after regression of age and gender.

Conflict of interest

The authors have no conflict of interest to declare.

Contributors

Mihailov A., Padula M.C., and Scariati E. designed the study; Padula M.C., Scariati E., Schaefer M. and Schneider M. acquired the magnetic resonance imaging and clinical data; Mihailov A. and Padula M.C. analyzed the data and conducted the statistical analysis; Eliez S., Scariati E. and Schaefer M. supervised the technical aspects of the data analysis; Mihailov A. and Padula M.C. wrote the first draft of the manuscript; all authors contributed to the interpretation of the results and the writing of the manuscript. All authors have approved the final manuscript.

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