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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.

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 gyrification 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 gyrification (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 gyrification) 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 gyrification 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

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