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# Developmental changes in multivariate neuroanatomical patterns that predict risk for psychosis in 22q11.2 deletion syndrome

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ABSTRACT

The primary objective of the current prospective study was to examine developmental patterns of voxel-by-voxel gray and white matter volumes (GMV, WMV, respectively) that would predict psychosis in adolescents with 22q11.2 deletion syndrome (22q11.2DS), the most common known genetic risk factor for schizophrenia. We performed a longitudinal voxel-based morphometry analysis using structural T1 MRI scans from 19 individuals with 22q11.2DS and 18 typically developing individuals. In 22q11.2DS, univariate analysis showed that greater reduction in left dorsal prefrontal cortical (dPFC) GMV over time predicted greater psychotic symptoms at Time2. This dPFC region also showed significantly reduced volumes in 22q11.2DS compared to typically developing individuals at Time1 and 2, greater reduction over time in 22q11.2DS $COMT^{Met}$ compared to $COMT^{Val}$, and greater reduction in those with greater decline in verbal IQ over time. Leave-one-out Multivariate pattern analysis results (MVPA) on the other hand, showed that patterns of GM and WM morphometric changes over time in regions including but not limited to the dPFC predicted risk for psychotic symptoms (94.7–100% accuracy) significantly better than using univariate analysis (63.1%). Additional predictive brain regions included medial PFC and dorsal cingulum. This longitudinal prospective study shows novel evidence of morphometric spatial patterns predicting the development of psychotic symptoms in 22q11.2DS, and further elucidates the abnormal maturational processes in 22q11.2DS. The use of neuroimaging using MVPA may hold promise to predict outcome in a variety of neuropsychiatric disorders.



## 1. Introduction

The 22q11.2DS, also known as velocardiofacial syndrome (Shprintzen et al., 1978), is the most common microdeletion syndrome in humans occurring in at least 1–5000 live births (Botto et al., 2003). It has been shown that at least 25% of individuals with 22q11.2DS develop a schizophrenia-like psychosis by young adulthood (Murphy et al., 1999). Being the most common identifiable genetic risk factor for schizophrenia, 22q11.2DS serves as an important model from which to elucidate the path leading from a well defined genetic defect to variation in brain development and eventually to the evolution of psychotic symptoms.

Research has shown links between the development of psychotic symptoms and VIQ decline or *catechol-O-methyltransferase* (*COMT*) hemizygosity (Gothelf et al., 2005), but no studies have demonstrated whether neuroanatomical patterns can predict the development of psychotic symptoms in 22q11.2DS. This may be due to the fact that past longitudinal studies have used univariate analysis of more crude volumetric or lobar volume measures (Gothelf et al., 2005) rather than multivariate analysis of voxel-based measures, which could be a more sensitive and powerful measure in detecting subtle regional changes. Indeed, studies have begun to elucidate neuroanatomical patterns that predict disease transition in at-risk mental states of psychosis (Koutsouleris et al., 2009). Therefore, the main purpose of the current study was to identify neuroanatomical patterns that predicted risk of psychotic symptoms with high accuracy using cross-validation support vector machine (SVM) algorithms and to compare that with univariate methods.

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## 2. Methods

### 2.1. Subjects

Time1 and Time2 data included 19 children with 22q11.2DS and 18 typically developing (TD) controls. The presence of the 22q11.2 microdeletion was confirmed in all subjects with 22q11.2DS by fluorescence in situ hybridization (FISH). All controls were screened and were not included in the study if they had a history of major psychiatric disorder or neurological or cognitive impairment. The follow-up interval was 4.9 ± 0.7 for the 22q11.2DS group and 4.9 ± 0.9 years for the controls. The demographic and clinical characteristics of the sample are presented in Table 1. None of the subjects had history of substance abuse and the sample was well matched across diagnostic groups in mean age, parents' years of education, male to female ratio, ethnicity, and handedness (Gothelf et al., 2007). None of the subjects had a psychotic disorder at Time1. In general, the 22q11.2DS group had significantly lower IQ scores compared to the TD group. There were also significant IQ interactions such that the TD group showed general increase while the 22q11.2DS group showed a general decrease in IQ over time.

By the time of the Time2 scan, 10 participants with 22q11.2DS had received atypical antipsychotics (6 subjects) or mood stabilizers (10 subjects) for more than six months. All 6 subjects receiving antipsychotics had a psychotic disorder. After providing a complete description of the study to the subjects and their parents, written informed consent was obtained at both time points, according to protocols approved by the institutional review board at Stanford University School of Medicine.

### 2.2. Genotyping

Blood samples were drawn from the 22q11.2DS group to determine genotype. The *COMT Val108/158Met* polymorphism (rs165688) was genotyped using a standard method (Lachman et al., 1996). Eleven individuals had $COMT^{Met}$ and eight had $COMT^{Val}$ genotypes. The demographic and clinical characteristics of the sample are presented in Tables 1 and 2.

### 2.3. Cognitive and psychiatric measures

Cognitive and psychiatric assessments were conducted at both time points. For the cognitive assessment, the Wechsler Intelligence Scale for Children, 3rd edition (WISC III) was used for subjects 17 years and younger and the Wechsler Adult Intelligence Scale, 3rd edition (WAIS III) was used for subjects older than 17 years. For screening of psychotic disorders, the Screening Question portion of the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SAD-PL) was used. In addition, subjects above the age of 18 years were also evaluated with the Structured Clinical Interview for DSM-IV Diagnoses (SCID). At Time2, all 22q11.DS individuals were tested by a child and adolescent psychiatrist, who completed the Brief Psychiatric Rating Scale (BPRS) to measure psychotic symptoms.

### 2.4. Magnetic resonance imaging (MRI) acquisition

All imaging data were acquired at the Richard M. Lucas Research Center (Stanford University, Palo Alto, CA USA) using the same Signa 1.5 T scanner (General Electric, Milwaukee, WI). Data were acquired at two time points with a slow spoiled gradient echo (SPGR) sequence: flip angle = 45°, repetition time (TR) = 6 s, echo time (TE) = 1 s, matrix size = 256 × 256, field of view (FOV) = 240 × 240 mm, pixel size = 0.9375 × 0.9375 mm, slice number = 124, thickness = 1.5 mm.

### 2.5. Image processing: voxel-based morphometry (VBM) analyses

VBM analyses of T1 MR images were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm) and VBM5.1 (http://dbm.neuro.uni-jena.de/vbm). T1 images were bias corrected, segmented to GM, WM and cerebrospinal fluid (CSF), spatially normalized and modulated, followed by smoothing with an isotropic Gaussian kernel with full-width at half-maximum (FWHM) of 12 mm. Since the results from standard and customized templates were essentially unchanged, the results from the standard template are reported here.

### 2.6. Statistical analysis

#### 2.6.1. Analyses of GM and WM volumes

We examined total GMV, WMV and total tissue volume (TTV, GMV + WMV) obtained from VBM analyses using repeated measures analyses of variance (ANOVA).

#### 2.6.2. VBM analysis

We examined regional GM and WM volume differences between 22q11.2DS and TD controls using whole-brain analysis of

**Table 1**
Demographic information for the 22q11.2DS and TD groups.

| | 22q11.2DS | | Controls | | ANOVA | | | *T*-test, Chi-square |
|---|---|---|---|---|---|---|---|---|
| | Time1 | Time2 | Time1 | Time2 | *P* (group) | *P* (time) | *P* (interaction) | *P* |
| N | 19 | | 18 | | | | | |
| Age | 13.05 | 17.92 | 13.40 | 18.31 | 0.78 | <0.001 | 0.90 | |
| | *3.96* | *3.81* | *4.04* | *4.48* | | | | |
| Gender (F:M) | 8:11 | | 8:10 | | | | | 0.89 |
| Handedness (Lt:Mixed:Rt) | 2:1:16 | | 0:0:18 | | | | | 0.21 |
| COMT (Met:Val) | 11:8 | | | | | | | |
| BPRS | | 36.32 | | | | | | |
| | | *12.59* | | | | | | |
| VIQ | 80.05 | 75.50 | 114.82 | 118.50 | <0.001 | 0.16 | 0.001 | 22q11.2DS Time1 > 2: 0.09 |
| | *14.31* | *15.40* | *8.52* | *10.44* | | | | Controls Time1 < 2: 0.04 |
| GMV [ml] | 795.98 | 760.87 | 872.49 | 833.27 | 0.006 | <0.001 | 0.74 | |
| | *80.61* | *89.85* | *70.45* | *78.44* | | | | |
| WMV [ml] | 389.81 | 410.89 | 438.49 | 450.91 | 0.02 | <0.001 | 0.17 | |
| | *55.56* | *57.05* | *54.06* | *51.12* | | | | |

*Italicized font*: Standard deviation.