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# Psychotic symptoms influence the development of anterior cingulate BOLD variability in 22q11.2 deletion syndrome

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ABSTRACT

Chromosome 22q11.2 deletion syndrome (22q11DS) is a neurodevelopmental disorder associated with a broad phenotype of clinical, cognitive and psychiatric features. Due to the very high prevalence of schizophrenia (30–40%), the investigation of psychotic symptoms in the syndrome is promising to reveal biomarkers for the development of psychosis, also in the general population. Since schizophrenia is seen as a disorder of the dynamic interactions between brain networks, we here investigated brain dynamics, assessed by the variability of blood oxygenation level dependent (BOLD) signals, in patients with psychotic symptoms. We included 28 patients with 22q11DS presenting higher positive psychotic symptoms, 29 patients with lower positive psychotic symptoms and 69 healthy controls between 10 and 30 years old. To overcome limitations of mass-univariate approaches, we employed multivariate analysis, namely partial least squares correlation, combined with proper statistical testing, to analyze resting-state BOLD signal variability and its age-relationship in patients with positive psychotic symptoms. Our results revealed a missing positive age-relationship in the dorsal anterior cingulate cortex (dACC) in patients with higher positive psychotic symptoms, leading to globally lower variability in the dACC in those patients. Patients without positive psychotic symptoms and healthy controls had the same developmental trajectory in this region. Alterations of brain structure and function in the ACC have been previously reported in 22q11DS and linked to psychotic symptoms. The present results support the implication of this region in the development of psychotic symptoms and suggest aberrant BOLD signal variability development as a potential biomarker for psychosis.



## 1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a neurodevelopmental disorder that comes with a vast cognitive and clinical phenotype (Oskarsdóttir et al., 2004; Maeder et al., 2016; Karayiorgou et al., 2010; McDonald-McGinn et al., 2015). The prevalence of schizophrenia in adult patients with the disorder is estimated at 30% to 40% (Murphy et al., 1999; Lewandowski et al., 2007; Schneider et al., 2014), which makes the deletion syndrome a model for the study of neurodevelopmental markers of psychosis and schizophrenia (Bassett and Chow, 1999).

Even though the exact neural mechanisms that may underlay the pathophysiology of psychosis and schizophrenia remain uncertain, schizophrenia is commonly seen as a disorder of functional network dysconnectivity rather than regionally specific pathophysiology (Friston et al., 1996; Friston, 1998). The recently proposed triple network model (Menon, 2011) sees mental disorders as a disruption of the interaction between three large scale brain networks in particular, namely the default mode network (DMN), the central executive network (CEN) and the salience network (SN). Findings in schizophrenia confirm and emphasize this hypothesis as a model for the disorder (Nekovarova et al., 2014). More precisely, structural and functional findings in the anterior cingulate cortex and the insula, two main regions of the SN (Nekovarova et al., 2014), suggest that disruptions in the SN mediate the altered relationship between DMN and CEN.

Since alterations in schizophrenia are obviously complex and more and more research confirms the impairment of brain dynamics in the disorder (Van Den Heuvel and Fornito, 2014), the investigation of brain dynamics in psychosis seems a promising approach

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when searching for neural correlates of its development. One simple approach to probe into dynamic brain function is moment-to-moment blood oxygenation level dependent (BOLD) signal variability (Garrett et al., 2013b). Even though it is not commonly considered in resting-state functional magnetic resonance imaging (fMRI) studies, its implication in development and cognitive performance suggests its importance for healthy brain function (Grady and Garrett, 2014). Indeed, higher temporal signal variability reflects a higher dynamic range and network complexity, which is crucial for the function of neural systems (Deco et al., 2009; 2011; Garrett et al., 2013b; McIntosh et al., 2010). Findings in electroencephalography (EEG), magnetoencephalography (MEG) and fMRI suggest that brain variability increases from child- to adulthood (McIntosh et al., 2008; Lippé et al., 2009; Misić et al., 2010; Miskovic et al., 2016; Zöller et al., 2017) and is reduced under anesthesia (Huang et al., 2016). Furthermore higher variability has been linked to better cognitive performance (Garrett et al., 2013a, 2014), cognitive flexibility (Armbruster-Genc et al., 2016) and better pain coping (Rogachov et al., 2016).

While there are several studies relating psychosis in 22q11DS to altered brain morphology and structural connectivity (Scariati et al., 2016), only few investigated brain function in relationship to psychosis (Debbané et al., 2012; Mattiaccio et al., 2016; Scariati et al., 2014; Padula et al., 2017; Tomescu et al., 2014). Two resting-state fMRI studies on whole brain functional connectivity linked increased DMN activity in 22q11DS to psychotic symptoms (Debbané et al., 2012; Mattiaccio et al., 2016). Padula et al., 2017 investigated functional connectivity within and between DMN, CEN and SN in 22q11DS, but did not find any significant relationship with psychotic symptoms. Using a multivariate approach, another resting-state fMRI study revealed a connectivity pattern that discriminated patients presenting prodromal positive symptoms (Scariati et al., 2014). The pattern included the anterior cingulate, right inferior frontal and left superior temporal cortices. Furthermore, an EEG study in patients with 22q11DS has linked altered SN function (i.e. the over-representation of EEG microstate C) to the presence of hallucinations (Tomescu et al., 2014; Britz et al., 2010).

While we already investigated BOLD signal variability alterations and development in 22q11DS (Zöller et al., 2017), to date no study has revealed its relationship to psychotic symptoms in 22q11DS. Here, we employed partial least squares correlation (PLSC; Krishnan et al., 2011) as a powerful multivariate approach to reveal alterations and age-relationship of BOLD variability related to psychotic symptoms in 22q11DS. We furthermore compared BOLD variability in patients with and without psychotic symptoms to healthy controls (HCs) to evaluate alterations intrinsic to the presence of psychotic symptoms.

## 2. Methods

### 2.1. Participants

In the present study, we included 57 patients with 22q11DS aged between 10 and 30 years and 69 HCs in the same age range. HCs were recruited amongst siblings of the patients and through the Geneva state school system. Within the group of patients with the microdeletion, psychotic symptoms were assessed using the Structured Interview of Prodromal Symptoms (SIPS; Miller et al., 2003). Patients with a score of >= 3 in at least one of the positive SIPS sub-scales (i.e. Unusual Thought Content, Suspiciousness, Grandiosity, Hallucinations, and Disorganised Communication) were considered as having attenuated positive symptoms aside the criteria of frequency and duration (Fusar-Poli et al., 2013). Amongst the patients with 22q11DS, 28 patients were diagnosed with at least attenuated positive symptoms (PS+), while the remaining 29 had low positive symptoms scores (<= 2) and were included in the PS−group. In the PS+ group, five patients were diagnosed with a psychotic disorder according to DSM-IV-TR criteria (see Supplementary Table S1). For more detailed demographic information, see Table 1. Written informed consent was received from participants and their parents (for subjects younger than 18 years old). The research protocols were approved by the Institutional Review Board of Geneva University School of Medicine. For a summary on criteria for the exclusion of subjects from our initial cohort and information on subjects included in our previous fMRI studies refer to Supplementary Materials.

### 2.2. Image acquisition

All MRI brain scans were acquired at the Centre d'Imagerie BioMédicale (CIBM) in Geneva on a Siemens Trio (N = 86: 53 HCs,

**Table 1**
Demographic information.

| | PS+ | PS− | HC | p-value PS+ vs. PS− | p-value PS+ vs. HC | p-value PS− vs. HC |
|---|---|---|---|---|---|---|
| Number of subjects (M/F) | 28 (12/16) | 29 (14/15) | 69 (30/39) | 0.6813 | 0.9554 | 0.6629 |
| Age mean±SD (range) | 17.93±4.50 (10.3–27.9) | 17.44±4.54 (11.1–28.4) | 17.60±5.22 (10.0–29.6) | 0.6846 | 0.7651 | 0.8918 |
| Right handed* | 60.71 % | 96.55% | 78.79 % | <0.001 | 0.0697 | 0.0288 |
| IQ** | 67.25±9.82 | 70.21±13.71 | 108.86±13.47 | 0.3563 | <0.001 | <0.001 |
| N. subjects meeting criteria for psychiatric diagnosis*** | 20 | 14 | N/A | | | |
| Anxiety disorder | 5 | 4 | N/A | | | |
| Attention deficit hyperactivity disorder | 1 | 1 | N/A | | | |
| Mood disorder | 2 | 3 | N/A | | | |
| Schizophrenia spectrum disorders | 2 | 0 | N/A | | | |
| More than one psychiatric disorder | 10 | 6 | N/A | | | |
| N. subjects medicated | | | | | | |
| Methylphenidate | 1 | 7 | 0 | | | |
| Antipsychotics | 3 | 0 | 0 | | | |
| Anticonvulsants | 1 | 0 | 0 | | | |
| Antidepressants | 3 | 1 | 0 | | | |
| More than one class of medication | 2 | 0 | 0 | | | |

* Handedness was measured using the Edinburgh laterality quotient, right handedness was defined by a score of more than 50. ** IQ was measured using the Wechsler Intelligence Scale for Children–III (Wechsler, 1991) for children and the Wechsler Adult Intelligence Scale–III (Wechsler, 1997) for adults. *** The presence of psychiatric disorders was evaluated during a clinical interview with the patients using the Diagnostic Interview for Children and Adolescents Revised (DICA-R; Reich, 2000), the psychosis supplement from the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1996).

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