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Disentangling resting-state BOLD variability and PCC functional connectivity in 22q11.2 deletion syndrome

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ABSTRACT

Although often ignored in fMRI studies, moment-to-moment variability of blood oxygenation level dependent (BOLD) signals reveals important information about brain function. Indeed, higher brain signal variability has been associated with better cognitive performance in young adults compared to children and elderly adults. Functional connectivity, a very common approach in resting-state fMRI analysis, is scaled for variance. Thus, alterations might be confounded or driven by BOLD signal variance alterations. Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a neurodevelopmental disorder that is associated with a vast cognitive and clinical phenotype. To date, several resting-state fMRI studies reported altered functional connectivity in 22q11.2DS, however BOLD signal variance has not yet been analyzed. Here, we employed PLS correlation analysis to reveal multivariate patterns of diagnosis-related alterations and age-relationship throughout the cortex of 50 patients between 9 and 25 years old and 50 healthy controls in the same age range. To address how functional connectivity in the default mode network is influenced by BOLD signal fluctuations, we conducted the same analysis on seed-to-voxel connectivity of the posterior cingulate cortex (PCC) and compared resulting brain patterns. BOLD signal variance was lower mainly in regions of the default mode network and in the dorsolateral prefrontal cortex, but higher in large parts of the temporal lobes. In those regions, BOLD signal variance was correlated with age in healthy controls, but not in patients, suggesting deviant developmental trajectories from child- to adulthood. Positive connectivity of the PCC within the default mode network as well as negative connectivity towards the frontoparietal network were weaker in patients with 22q11.2DS. We furthermore showed that lower functional connectivity of the PCC was not driven by higher BOLD signal variability. Our results confirm the strong implication of BOLD variance in aging and give an initial insight in its relationship with functional connectivity in the DMN.

1. Introduction

Inter- and intra-subject variability of resting-state functional magnetic resonance imaging (rs-fMRI), such as between-trial variability (Poldrack et al., 2015; Laumann et al., 2015; Davis et al., 2014), spatial variability between voxels (Davis et al., 2014; Gopal et al., 2016) and moment-to-moment variability of blood oxygenation level dependent (BOLD) signals within every voxel (McIntosh et al., 2010; Deco et al., 2011; Allen et al., 2014) have gained interest in recent literature. Such variability measures are rarely taken into account in conventional rs-fMRI analysis, but their consideration might give a deeper insight into underlying brain processes and their connection to disease-related alterations (McIntosh et al., 2010; Gopal et al., 2016). Even though the exact implications of the latter, moment-to-moment BOLD signal variability, are not clear yet, theoretical work has suggested that spontaneous signal fluctuations are crucial for neural system functions

Abbreviation: 22q11.2DS, chromosome 22q11.2 deletion syndrome; ALFF, amplitude of low-frequency fluctuations; BOLD, blood oxygenation level dependent; DARTEL, Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; DMN, default mode network; DPARSF, Data Processing Assistant for Resting-State fMRI; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; FWHM, full width half maximum; HC, healthy control; IBASPM, Individual Brain Atlases using Statistical Parametric Mapping; LV, latent variable; MEG, magnetoencephalography; PCC, posterior cingulate cortex; PLS, partial least squares; rs-fMRI, resting-state functional magnetic resonance imaging; RSN, resting-state network; SD_{BOLD}, BOLD signal standard deviation; SVD, singular value decomposition

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and reflect larger network complexity and dynamic range (Deco et al., 2011; McIntosh et al., 2010). Several studies focusing on the implications of BOLD signal variability on aging and cognitive performance in adults have demonstrated that moment-to-moment variability is not just noise as previously assumed, but is higher in better performing, younger adults compared to lower performing, elderly subjects (Garrett et al., 2013a, 2014; Grady and Garrett, 2014). Findings in other modalities such as EEG (McIntosh et al., 2008; Lippé et al., 2009) and MEG (Misić et al., 2010) support those findings, suggesting lower brain variability in children compared to young adults. Moment-to-moment BOLD signal fluctuations have been shown to be altered in multiple neuropsychiatric disorders such as autism (Di Martino et al., 2014; Lai et al., 2010), Alzheimer's disease (Zhao et al., 2014; Liu et al., 2014; Han et al., 2011; Xi et al., 2012) and attention deficit hyperactivity disorder (Zang et al., 2007), as well as schizophrenia (Yu et al., 2014; Yang et al., 2014; Liu et al., 2016). The strong relationship of BOLD signal variability with age and cognitive performance make this approach especially promising to obtain further insight in the mechanisms driving the development of cognitive and psychiatric disorders.

Rs-fMRI has been widely used in recent years to analyze altered brain function in numerous psychiatric diseases. It is especially advantageous when studying populations with limited abilities to respond to task, such as young children or individuals with impaired cognitive functions and attention deficits. Most rs-fMRI studies focus on stationary functional connectivity, assessed by computing the temporal correlation between the BOLD signals of different brain regions computed over the whole resting-state session. However, conventional functional connectivity is normalized for BOLD signal variance. In other words, the Pearson correlation coefficient is scaled with respect to individual signal standard deviation and BOLD signal variability might even confound results of functional connectivity (Garrett et al., 2013b). For instance, lower functional connectivity might result from higher variance, or oppositely, lower variance might have weakened the effect of functional connectivity reduction.

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a neurodevelopmental disorder caused by a microdeletion in chromosome 22. It occurs in approximately 1 out of 4000 live births and comes with a vast phenotype that includes somatic, cognitive and psychiatric features (Oskarsdóttir et al., 2004). Amongst others, patients with 22q11.2DS suffer from a wide range of cognitive impairments, including mild mental delay and impaired executive functions (Maeder et al., 2016; Antshel et al., 2008; Niklasson and Gillberg, 2010; Swillen et al., 1997). Furthermore, 22q11.2DS comes with a very high risk of developing schizophrenia, which occurs in 30% to 40% of patients (Lewandowski et al., 2007; Murphy et al., 1999; Schneider et al., 2014). The developmental characteristics of the disease and the high risk of psychotic symptoms makes 22q11.2DS a unique model for the study of behavioral, clinical and neural markers in schizophrenia in order to improve treatments and prevention (Bassett and Chow, 1999).

In 22q11.2DS, to date, several studies have analyzed functional connectivity during rest (Debbané et al., 2012; Padula et al., 2015; Scariati et al., 2014; Schreiner et al., 2014; Mattiaccio et al., 2016). They have revealed altered connectivity in multiple resting-state networks (RSNs) such as the visuospatial, sensory-motor and default mode networks. Two of the studies (Padula et al., 2015; Schreiner et al., 2014) specifically focused on connectivity of the default mode network (DMN), a RSN that has been associated with self-referential, autobiographical mental processes and social cognition (Greicius et al., 2003; Fair et al., 2008; Qin and Northoff, 2011). They revealed decreased connectivity in 22q11.2DS, especially between anterior-posterior regions (Schreiner et al., 2014; Padula et al., 2015). Alterations within the DMN have furthermore been associated with dysfunctional social behavior (Schreiner et al., 2014) as well as psychotic symptoms (Debbané et al., 2012; Mattiaccio et al., 2016).

To our best knowledge, no studies to date have investigated BOLD signal variability in 22q11.2DS. Given its link to development and cognition, we hypothesize that BOLD signal variability is broadly altered in 22q11.2DS and that it is increasing during development from child- to adulthood. We used the BOLD signal standard deviation (SD_{BOLD}) to measure brain variability. We then employed multivariate partial least squares (PLS) correlation (Krishnan et al., 2011; McIntosh et al., 2004) in order to identify multivariate brain variability alterations and developmental characteristics in our 22q11.2DS cohort compared to controls. PLS correlation is better suited for voxelwise brain analysis than mass-univariate approaches, as they assume independence between all voxels (a hypothesis which is obviously wrong in the brain) and are thus very limited by the problem of multiple comparisons. PLS correlation measures multivariate relationship between two sets of variables (here: voxelwise SD_{BOLD} on one side and a combination of subject-specific design variables, i.e. diagnosis, age and age by diagnosis interaction, on the other side). Its second advantage in addition to multivariability of the brain pattern is thus the possibility to investigate the relationship of brain data with multiple external variables at the same time. We secondly hypothesize that conventional functional connectivity analysis might be influenced by BOLD variation, as Pearson correlation is normalized for standard deviation. To obtain an insight on possible links between functional connectivity and brain variability, we selected a seed inside the posterior cingulate cortex (PCC) and analyzed brain-wide seed-to-voxel connectivity. The PCC was selected as it is a central hub inside the DMN, one of the best studied RSN (Greicius et al., 2003; Fair et al., 2008; Menon and Uddin, 2010). It additionally appeared as a region of strongly decreased SD_{BOLD} variability during the first analysis. We used the same PLS approach as before to identify multivariate alterations and age-relationship of PCC functional connectivity. In a last step we identified regions where both functional connectivity and BOLD signal variance were altered in our cohort. In those regions, SD_{BOLD} might confound or even drive functional connectivity alterations. Thus, we compared the direction of alteration of both measures in those regions, in order to obtain a first insight in the relationship between BOLD variability and functional connectivity.

2. Methods

2.1. Participants

Fifty patients with 22q11.2DS aged between 9 and 25 (M/F=21/29, mean age=16.53 ± 4.25 years) were included in the study (see Table 1). The control group comprised fifty healthy subjects in the same age range (M/F=22/28, mean age=16.44 ± 4.20 years). Healthy controls (HCs) were recruited amongst siblings of our patients and through the Geneva state school system.

From our initial sample of 110 patients and 75 HCs between 9 and 25 years old, a total of 85 participants had to be excluded to ensure the good quality of the data. Five subjects (only patients) were excluded because they reported having fallen asleep during the scanning session. Another 34 subjects (5 HC) had to be excluded due to excessive motion of more than 3 mm in translation or 3° in rotation and the data of 35 more subjects (19 HC) were not used because parts of the cortex were not captured. From the remaining dataset, 11 more participants (1 HC) were excluded after motion scrubbing (Power et al., 2012, see paragraph *Preprocessing*) as less than 100 rs-fMRI scans, corresponding to 4 min of scanning time, had a framewise displacement below the threshold of 0.5 mm. Table 2 shows a summary of motion data within the two groups.

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. The cohort is partly overlapping with our previous rs-fMRI studies: 33 subjects (15 HC) have been also included in Debbané et al. (2012), 52 subjects (27 HC) in Scariati et al.