Short communication

Hypogyriﬁcation and its association with cognitive impairment in children with 22q11.2 deletion Syndrome: A preliminary report

Olivia Lutz a,⁎, Paulo Lizano a,b, Suraj Sarvode Mothi b, Adam Joseph a, Neeraj Tandon a, Leighanne Ormston a, Stephen Hooper c, Matcheri Keshavan a,b, Vandana Shashi d

⁎ Corresponding author.
E-mail address: olutz@bidmc.harvard.edu (O. Lutz).

22q11.2 Deletion Syndrome (22qDS) is a neurogenetic disorder resulting in cognitive deﬁcits and hypogyriﬁcation, but relationships between these processes have not been established. 22qDS youth and healthy controls (HC) were administered a battery of cognitive tasks. Gyrification measurements were extracted from structural T1 scans using Freesurfer, contrasted between groups, and correlated to cognition. Data was adjusted for age, sex, socio-economic status and intracranial volume. 22qDS displayed signiﬁcant hypogyriﬁcation which was associated with poorer executive functioning and verbal learning in orbitofrontal and anterior cingulate cortex. Our preliminary ﬁndings identiﬁed neurodevelopmental deﬁcits in 22qDS shown by hypogyria, which relate to cognitive impairments.

1. Introduction

22q11.2 Deletion Syndrome (22qDS), also known as velocardiofacial syndrome, is a neurogenetic disorder caused by a hemizygous microdeletion of 1.5–3 megabases (Mb) on chromosome 22 and results in medical manifestations including congenital heart disease and immune dysfunction (Shprintzen, 2008; Tezenas Du Montcel et al., 1996). 22qDS has been associated with abnormalities in motor development, learning, intelligence, and behavior (Shprintzen, 1999; Swillen et al., 1998). Individuals with 22qDS have a greater risk factor for psychiatric disorders with executive functioning deﬁcits such as autism and schizophrenia (Schneider et al., 2014). Approximately 25–32% of individuals with 22qDS develop psychosis (Green et al., 2009; Murphy et al., 2000), thus is an important model for studying genetic risk factors for psychosis.

Gyrification (cortical folding) is important for understanding the neurodevelopmental markers of psychosis and has been proposed as an endophenotype for psychosis (Nanda et al., 2014; White and Gottesman, 2013). Gyrification develops when neuronal migration and proliferation processes are complete (Gertz and Kriegstein, 2015; Neal et al., 2006). Disruptions in these processes impact human sulcal and gyral patterns (Rakic, 1995; Stewart et al., 1975) and have been demonstrated in 22qDS mouse models (Maynard et al., 2003; Meechan et al., 2009). These reported disruptions suggest a plausible cause for gyrification alterations shown in MRI studies of 22qDS patients (Karayiorgou et al., 2010). Hypogyriﬁcation has been consistently reported in 22qDS (Kunwar et al., 2012; Schaer et al., 2006), speciﬁcally in regions including the midline cortex (medial prefrontal, cingulate, precuneus, and orbitofrontal) as well as middle frontal, inferior frontal gyrus, motor and parietal cortex (Schaer et al., 2009; Schmitt et al., 2015; Srivastava et al., 2011).

While gyrification alone has been examined in individuals with neurodevelopmental disorders, including 22qDS, its relationship to cognition has not been well documented. Despite some studies showing that higher gyrification is associated with better cognition in healthy individuals (Chung et al., 2017; Gregory et al., 2016), this finding has not been replicated in 22qDS. Though one study reported increased occipital gyral complexity in 22qDS compared to controls, there were no signiﬁcant relationships to IQ (Bearden et al., 2009). To our knowledge, no studies have reported the relationships between gyrification and cognition in 22qDS. Our goals are to: 1. Investigate gyrification in 22qDS youth compared to healthy children in regions typically reported in the literature (bilateral anterior cingulate (ACC), superior frontal, dorsal lateral prefrontal cortex (DLPFC), medial and lateral orbitofrontal (mOFC and IOFC), precuneus and superior parietal cortex) and 2. Assess their relationship to cognition (executive...
functioning, verbal memory, fine-motor sequencing and set-shifting, and attention). We predict that these regions will show hypogyri
cification and will associate with poorer cognition in 22qDS youth.

2. Material and methods

2.1. Participants

Children diagnosed with 22qDS with no history of psychosis (n = 16) were age-matched to healthy controls (HC, n = 22).

The measurement battery included previously reported cognitive tasks that showed impairments in 22qDS (Hooper et al., 2013): WISC-IV Full-Scale IQ, Continuous Performance Task (CPT) Fast and Slow Numbers d’, California Verbal Learning Test (CVLT) Children’s Version Total Z score, fine-motor sequencing and set-shifting (Trail Making Test A and B), and Wisconsin Card Sorting Test (WCST) Categories Complete (CC) and Perseverative Errors (PE) Standard Scores (higher scores indicating better performance).

2.2. Imaging

T1 Spoiled GRASS (3T) images were processed using Freesurfer 4.3 to obtain local gyri
cification index (LGI) (Schaer et al., 2008). LGI was calculated using the ratio of the surface area of cortex within the sulcal folds compared to the surface area of cortex on the outer surface (Schaer et al., 2008). LGI values range from one to five such that lower cortical folding (hypogyri
cification) would have a smaller gyri
cification index and would correspond to abnormal neurodevelopment. ACC LGI was calculated by averaging the rostral and caudal anterior cingulate cortex and DLPFC LGI by averaging the rostral and caudal middle frontal cortex.

2.3. Statistical analysis

Demographic variables were compared between groups via chi-squared tests and t-tests. LGI contrasts between 22qDS and HC were examined using an analysis of covariance. Significant regions (p < 0.05, corrected) were assessed in the secondary analysis in relation to cognition using partial Spearman correlations. Neurocognitive relationships with significant LGI regions were evaluated within its respective category: IQ, attention and executive functioning (CPT), fine-motor sequencing and set-shifting (Trail Making Test), verbal memory (CVLT), and executive functioning (WCST).

All data were adjusted for age, sex, and socioeconomic status (SES), and LGI was also adjusted for total intracranial volume (ICV). Correlations were reported with and without IQ as a covariate. False Discovery Rate (FDR) correction was performed across seven regions (within hemisphere) for group contrasts. Partial correlations were FDR corrected for significant LGI regions (bilateral mOFC, left ACC, right superior frontal, and right IOFC) by cognitive domains (IQ, CPT, Trail Making Test, CVLT, WCST). Effect sizes were calculated using Cohen’s d.

Refer to supplementary methods for more information pertaining to inclusion criteria, neurocognitive testing, imaging and statistical analyses.
3. Results

3.1. Demographics

Our sample contained 16 22qDS (8 males, 8 females, 11.25 ± 1.86 years old) and 22 HC (8 males, 14 females, 12 ± 1.39 years old; Supplementary Table 1). The groups showed no significant sex, age, or ICV differences, but 22qDS showed significantly lower SES than HC (F = 12, p < 0.01).

3.2. Group differences

22qDS showed significantly (p < 0.05, corrected) lower LGI compared to HC in the mOFC (bilateral), left ACC, right superior frontal, and right IOFC (Fig. 1B). These regions were then included in the secondary analysis. LGI group differences that were significant before multiple comparisons are listed in supplementary results.

3.3. LGI and cognition correlations

In 22qDS youth, higher LGI in left ACC, left mOFC, right superior frontal, and right IOFC significantly correlated with higher IQ (p < 0.05, corrected, Fig. 1C, Supplementary Table 3). In 22qDS youth, higher left ACC and mOFC LGI was significantly (p < 0.05, corrected) associated with higher WCST CC and (Fig. 1D, Supplementary Table 4). Poorer performance in WCST PE significantly correlated (p < 0.05, corrected) with lower right mOFC and IOFC LGI (Fig. 1E, Supplementary Table 4). 22qDS youth also showed significant associations (p < 0.05, corrected) between both the higher left mOFC and left ACC LGI and better CVLT performance (Fig. 1F, Supplementary Table 5). After including IQ as a covariate, LGI was not significantly related to WCST or CVLT (data not shown).

In HC, no significant correlations between gyriﬁcation and cognitive function or intelligence were observed (see Supplementary Tables 3–5 for LGI correlations with IQ, WCST and CVLT).

Additional correlations that are signiﬁcant before multiple comparison correction in 22qDS youth and HC between LGI and IQ, Trail Making Test Parts A and B, CPT, and WCST are described in Supplementary Results.

4. Discussion

In our study, 22qDS youth displayed hypogyrification compared to HC in bilateral mOFC, right IOFC, left ACC, and right superior frontal cortex. In 22qDS youth, higher LGI in left ACC, left mOFC, right superior frontal, and right IOFC signiﬁcantly correlated with higher IQ. Better executive functioning associated with increased gyriﬁcation in the bilateral mOFC, right IOFC, and left ACC signiﬁcantly correlated with improved IQ. Better verbal learning performance correlated to increased left mOFC and left ACC gyriﬁcation and these results were no longer signiﬁcant after controlling for IQ. In HC, no signiﬁcant gyriﬁcation-cognition relationships were observed.

Our observation that 22qDS youth show hypogyrification in the medial prefrontal and lateral orbitofrontal cortex is consistent with previous hypogyrification ﬁndings in the medial frontal and parietal cortex (Schaer et al., 2006; Schmitt et al., 2015; Srivastava et al., 2011). With regards to a neurobiological mechanism, 22qDS animal models showed neuronal migration disruptions after a 1.5Mb deletion (Maynard et al., 2003; Meechan et al., 2009; 2012). Separate studies have shown that neuronal migration lays a foundation for gyriﬁcation in ferrets (Neal et al., 2006), and both pachygryria and lissencephalia are associated with reduced cortical neuronal migration in humans (Guerrini and Marini, 2006; Sheen et al., 2006). We infer that 22qDS in humans results in neuronal migration disruptions, leading to gyriﬁcation abnormalities. Furthermore, Cao et al. observed a logarithmic decrease in human gyriﬁcation using in vivo MRI in ages 4 to 83 such that patients with schizophrenia show accelerated reductions in dorsal lateral prefrontal cortex, ACC and supramarginal cortex (Cao et al., 2017).

Our data supports that patients’ with 22qDS show hypogyrification at a young age, suggesting that accelerated gyriﬁcation reductions may have important implications in the onset of psychosis.

To our knowledge, we are the ﬁrst study to report that hypogyrification associates with poorer cognition in 22qDS youth, which have been reported in other populations with neurocognitive deﬁcits like Prader-Willi Syndrome (Lukoshe et al., 2014). Additionally, a LdDel (Large Deletion) mouse model of 22qDS displayed diminished cortical circuit elements (interneurons, synaptic terminals and projection neurons) in the medial anterior frontal cortex, and the altered projection neuron frequencies predicted subsequent executive functioning deﬁcits in affected mice (Meechan et al., 2015). Given that both a diminished 22q11 dosage alters cortical circuitry and reduces gyriﬁcation, and these neurodevelopmental ﬁndings have demonstrated associations with cognition, subsequent studies should replicate these ﬁndings in humans and other animal models with human-like gyriﬁcation patterns such as ferrets (Neal et al., 2006). Our gyriﬁcation-cognition relationships were no longer signiﬁcant after controlling for IQ in 22qDS youth, which could be explained by the collinearity between IQ and cognition (Dennis et al., 2009). Therefore, controlling for IQ in a neurodevelopmental population with cognitive deﬁcits is likely to remove any major source of variance contributed by cognition (Dennis et al., 2009).

Previous studies have reported gyriﬁcation-cognition relationships in healthy adolescents (Chung et al., 2017; Gregory et al., 2016); however, we observed no such relationships in HC. Decreases in gyriﬁcation during adolescence may reﬂect the emergence of higher cognitive functions such that cognitive-gyriﬁcation relationships are strengthened during mid-adolescence (Chung et al., 2017; White et al., 2010). Our HCs’ ages ranged 9.12–14.44 years, so it is possible that these relationships will not mature until later in neurodevelopment. Furthermore, longitudinal gyriﬁcation in 22qDS youth remains lower than in healthy controls throughout childhood and adolescence (Kates et al., 2011; Kunwar et al., 2012), suggesting abnormal neurodevelopment that may lead to incomplete maturation that could underlie cognitive dysfunction.

Our work suggests that cognitive deﬁcits observed in 22qDS youth are associated with underlying gyriﬁcation abnormalities. Adolescence is a crucial period for cognitive development, and is also a time where the incidence of psychosis begins to increase. Cognitive decline has shown to be a predictive factor in conversion to psychosis in 22qDS (Antshel et al., 2017; Tang and Gur, 2017) as well as gyriﬁcation in relation to psychotic symptoms (Kunwar et al., 2012), but the latter has not been largely replicated. We acknowledge our limitations; we had a small sample size with cross-sectional data, so we could not assess longitudinal gyriﬁcation-cognitive relationships. Future studies should investigate gyriﬁcation-cognition relationships in 22qDS youth across all stages of development using larger sample sizes, in longitudinal studies, as well as in later adolescence and examine how these associations may differentiate those who convert to psychosis.

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Contributors

VS, MK and SH designed and implemented the study and both VS
and SH supervised data collection. AJ and NT were involved in quality control and data processing in Freesurfer. SSM, PL, and NT assisted OL with statistical analyses. OL wrote the manuscript with the help of LO, PL, NT and SSM. All authors provided feedback on data interpretation and have approved the final article.

Conflict of Interest
The authors declare no conflict of interest.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.007.

References


