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Brief report

Gyrification differences in children and adolescents with velocardiofacial syndrome and attention-deficit/hyperactivity disorder: A pilot study

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ABSTRACT

We used magnetic resonance imaging to investigate brain gyrification patterns between 19 children with attention-deficit/hyperactivity disorder (ADHD), 9 children with velocardiofacial syndrome (VCFS), and 23 control children. We found that VCFS is associated with widespread decreases in gyrification. In ADHD, we found minor differences from control children. No evidence was found for common gyrification patterns between VCFS and ADHD children.

1. Introduction

Children with velocardiofacial syndrome (VCFS) are at high risk for developing severe psychiatric disorders during their lifetime. The first presentation of symptoms often occurs during the school-age years when it is not uncommon for these children to have symptoms similar to attention-deficit/hyperactivity disorder (ADHD) (Shprintzen, 2000). However, while the inattention and impulsive behavior seen by some children with VCFS is characteristically similar to symptoms in children with ADHD only, it is unclear if there is overlap in the neurobiology of the two disorders.

Magnetic resonance imaging (MRI) techniques can evaluate specific neurobiological attributes of psychiatric disorders. One such attribute is brain gyrification. There have been few studies evaluating gyrification in VCFS or ADHD, and no studies comparing the two disorders. Also, the findings within each of these disorders are mixed. The most consistent findings in VCFS are decreased gyrification in the frontal and parietal lobes (Schaer et al., 2006; Kunwar et al., 2012; Srivastava et al., 2012) and decreased gyrification in occipital and midline regions of the brain (Srivastava et al., 2012). Findings in studies of ADHD show either a global decrease in cortical folding (Wolosin et al., 2009) or no abnormalities (Shaw et al., 2012). The mixed findings could be attributed to different methodological approaches, as different techniques were applied to measure gyrification.

The goal of this study was to use the same methodological approach in children with VCFS, children with ADHD, and matched control children to examine the similarities and differences in gyrification.

2. Methods

2.1. Participants

We studied 19 children with ADHD (16 boys), 9 with VCFS (5 boys), and 23 matched controls (12 boys). Mean ages were 15.4 (range 12–19), 13.6 (range 10–18),

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and 14.8 (range 9–19), respectively. Deletions in 22q11.2 were confirmed using a fluorescence in situ hybridization test, and psychiatric diagnoses were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-age Children (Kiddie-SADS) (Kaufman et al., 1997). All VCFS children showed (sub) clinical ADHD symptoms. Both informed consent and (for minors) assent was obtained. The study was approved by the Institutional Review Board at the University of Minnesota.

2.2. Magnetic resonance data acquisition

MR images were acquired with a 3 T Siemens MR System (Erlangen, Germany) using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (repetition time/echo time=2530/3.81, flip angle=7, field of view=160 mm, in-plane resolution of 0.625 × 0.625 × 1.5 mm, number of excitations=1) and an eight-channel head coil.

The pre-processing of the imaging data was performed using the FreeSurfer software program (http://surfer.nmr.mgh.harvard.edu/). Gyrification indices were computed using a novel three-dimensional geometric approach for the automatic computation of global and regional gyrification indices (GI) (Su et al., 2013).

2.3. Statistical analysis

Evaluation of gyrification was performed in a step-wise fashion to reduce multiple testing. Analyses of covariance (ANCOVAs) were used to assess global differences in GI between the hemispheres. If differences were found, these were followed up evaluating lobar differences. Also, post hoc testing of contrasts was performed. Given significant laterality and gender differences, GI was assessed separately between hemispheres, and gender was used as a covariate, as well as age.

A statistical threshold of $P < 0.05$ was used and Šidák correction was applied to correct for multiple testing. To account for lack of independence, we calculated the effective number of tests (M_{eff}) (Galwey, 2009). This formula yielded an effective number of 8.56 tests. Accordingly, we adapted the Šidák correction

$$\rho_{\min,\text{corrected,adjusted}} = 1-(1-\rho_{\min})^{Meff},$$

where $p_{\min}$ is the uncorrected P-value and $p_{\min,\text{corrected,adjusted}}$ is the P-value corrected for the number of effective tests. Effect sizes in the post hoc analyses were calculated using Cohen's d (Cohen, 1988).

3. Results

The 3 (diagnosis) by 2 (gender) ANCOVAs of gyrification with age as a covariate showed significant differences in both the left ($F_{2,46}=7.2$, $P=0.002$) and right ($F_{2,46}=5.0$, $P=0.01$) global measures of gyrification. Next, right and left lobar measures were explored separately. These ANCOVAs showed group differences in the left frontal ($F_{2,46}=9.0$, $P=0.0005$), the left medial temporal ($F_{2,46}=3.3$, $P=0.04$), and the left occipital lobes ($F_{2,46}=9.4$, $P=0.0004$). The left frontal and occipital lobes survived correction for multiple testing. In the right hemisphere, we found group differences in the right frontal lobe ($F_{2,46}=5.3$, $P=0.008$), the right parietal lobe ($F_{2,46}=5.9$, $P=0.005$), the right occipital lobe ($F_{2,46}=3.2$, $P=0.05$), and the right cingulate ($F_{2,46}=6.0$, $P=0.005$). The right parietal lobe and the cingulate cortex survived correction for multiple testing. Controlling for age alone yielded similar results.

Table 1 presents post hoc analyses showing differences between the individual groups.

4. Discussion

We found that VCFS children had significantly less gyrification in multiple brain regions than both children with ADHD and typically developing children. Children with VCFS demonstrated decreased GI in the frontal and parietal lobes, and cingulate cortex bilaterally, and the left occipital lobe compared with typically developing children. Compared with children with ADHD, children with VCFS showed bilateral decreases in the frontal, parietal, and occipital lobes, and the right cingulate cortex.

Similar to our findings, Schaer et al. (2006) observed decreased GI in VCFS children in the frontal and parietal lobes. Unlike our study, however, they did not find differences in the occipital lobe. Differences in surface morphology in the occipital lobe have been described in VCFS children (Bearden et al., 2009). We also showed significant decreases in the GI in the right and left cingulate cortex in VCFS children, which has not been reported previously.

In children with ADHD, we found an increased GI in the left medial temporal lobe. Interestingly, a delay in maturation of the cortex has been described in ADHD (Shaw et al., 2007). Since GI measures have been shown to decrease with development (White et al., 2010), one explanation could be that there is a delayed maturation in this lobe, which results in a relative increase in GI.

A limitation of our study is the small sample of VCFS children. However, in spite of the small sample size, statistically significant differences were seen in GI between the VCFS children compared with both typically developing controls and children with ADHD. Also, the effect sizes of the differences were large. Furthermore, we used a three-dimensional gyrification measure that is anatomically based, possibly providing greater power to detect differences.

In summary, we found a global decrease in gyrification in both hemispheres in a small sample of VCFS children. The decrease in gyrification was predominantly located in the frontal, parietal, and

Table 1
Group Contrasts Gyrification Index.

	ADHD vs. controls			VCFS vs. controls			ADHD vs. VCFS		
ROI	*F*	*P*	Effect size[a]	*F*	*P*	Effect size[a]	*F*	*P*	Effect size[a]
Global measures									
Left	0.00	0.97	0.08	12.41	**0.002**	1.12	9.27	**0.006**	1.24
Right	0.34	0.57	0.19	6.87	**0.01**	0.84	10.56	**0.003**	1.29
Lobar measures									
Left frontal	0.05	0.83	0.12	15.03	**0.0006**	1.22	15.52	**0.0006**	1.54
Right frontal	0.27	0.61	0.06	6.17	**0.02**	0.77	18.84	**0.0002**	1.46
Left parietal	0.44	0.51	0.15	4.68	**0.04**	0.66	4.84	**0.04**	0.71
Right parietal	1.49	0.23	0.36	6.04	**0.02**	0.77	13.20	**0.001**	1.08
Left temporal	0.14	0.71	0.33	1.18	0.29	0.31	0.11	0.74	0.00
Right temporal	0.03	0.86	0.07	0.01	0.93	0.00	0.02	0.88	0.07
Left medial temporal	7.20	**0.01**	0.88	0.10	0.76	0.04	2.14	0.16	0.67
Right medial temporal	0.22	0.64	0.26	0.04	0.85	0.17	0.31	0.58	0.09
Left occipital	0.22	0.64	0.03	16.11	**0.0004**	1.62	11.25	**0.003**	1.63
Right occipital	1.31	0.26	0.47	2.05	0.16	0.52	6.34	**0.02**	1.11
Left cingulate	0.00	0.96	0.02	11.72	**0.002**	1.33	1.88	0.18	0.92
Right cingulate	0.48	0.49	0.26	10.81	**0.003**	1.26	5.01	**0.03**	1.30

ADHD, Attention-deficit/hyperactivity disorder. VCFS, Velocardiofacial Syndrome.

[a] Effect sizes presented as Cohen's *d*, pooled standard deviations were used in the calculation. Significant results are highlighted in bold.

occipital lobes and the cingulate cortex. In children with ADHD, we found increased gyrification in the left medial temporal lobe. We found no evidence for a common pattern of brain gyrification between ADHD and VCFS children.

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