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## Associations between Performance on the Rey-Osterrieth Complex Figure and Regional Brain Volumes in Children with and without Velocardiofacial Syndrome

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### Abstract

Ninety-two children with velocardiofacial syndrome (VCFS), a genetic disorder caused by a microdeletion of chromosome 22q11.2 and an age, race and gender-ratio comparable sample of 59 control participants were included in the project. Participants received a MRI as well as a comprehensive neuropsychological battery; the primary outcome measure in the current report is the Rey-Osterrieth Complex Figure (ROCF). Children with VCFS performed less well on the ROCF and have lower whole brain volume compared to controls. After controlling for whole brain volume differences, children with VCFS have bilaterally less parietal lobe gray and white matter yet more frontal lobe white matter. Brain - behavior relationships include: (a) for both groups, parietal volumes (both gray and white matter) predicted ROCF Copy Organization performance and frontal volumes (both gray and white matter) predicted ROCF Copy Accuracy performance; (b) for controls, frontal white matter also predicted ROCF Copy Organization performance; (c) ROCF Recall Organization performance was best predicted by frontal gray matter volume only in our controls; ROCF Recall Accuracy performance was best predicted by frontal gray matter volume in both groups; and (d) in children with VCFS, performance on the ROCF-Copy Structural Elements Accuracy scale was predicted by right hemisphere white matter volume. Our hypotheses were also retested using IQ-matched and whole brain volume-matched subsamples. Identical results were obtained in these analyses. Assumptions about the organization of and the localization of the brain structures that subserved specific cognitive functions in the typically developing brain may not apply in the abnormally developing brain.

### Keywords

VCFS; 22q11.2 deletion syndrome; Rey-Osterrieth Complex Figure; brain-behavior associations

Velocardiofacial syndrome (VCFS), a chromosomal deletion disorder of 22q11.2 (3 Mb, 25-30 genes) affects 1 in 2000-5000 individuals (Shprintzen, 2005). The deletion syndrome is associated with multiple congenital anomalies, including cardiac malformations, hearing loss, hypocalcaemia, velopharyngeal insufficiency and cleft palate (Ryan et al., 1997). Phenotypic facial abnormalities include a long face, pear-shaped nose, small ears with overfolded helices, and vertically narrow eyes (Antshel et al., 2005). VCFS is associated with cognitive and developmental delays and the vast majority of children with VCFS experience academic difficulties, especially in math (Simon et al., 2002; Swillen et al., 1997; Swillen et al., 1999). Executive functioning deficits including difficulties shifting attention and a poorly developed working memory have also been indicated (Woodin et al., 2000). Most, but not all, children with VCFS exhibit deficits in abstract and nonverbal reasoning and visuospatial abilities (Moss et al., 1999). Some have hypothesized that VCFS is an exemplar of the nonverbal learning disability (NLD; Rourke et al., 2002; Swillen et al., 1999).

The VCFS behavioral phenotype includes poor social skills, introversion, disinhibition, impulsivity, anxiety and emotional instability (Papolos et al., 1996; Swillen et al., 2000). Attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric morbidity in children with VCFS, affecting approximately one-third to two-fifths of children (Antshel et al., 2006; Gothelf et al., 2004a). In addition to ADHD, mood, anxiety and oppositional defiant disorders are observed at increased prevalence rates compared to the general population (Antshel et al., 2006; Feinstein et al., 2002; Gothelf et al., 2004b; Papolos et al., 1996; Vogels et al., 2002). Furthermore, individuals with VCFS may be predisposed to psychiatric conditions in adulthood, most commonly schizophrenia (Shprintzen et al., 1992; Murphy, Jones, & Owen, 1999).

Although there are some inconsistencies in the neuroimaging data, several findings that focus on cortical alterations in children with VCFS have been reported consistently. Whole brain volume is roughly 11% less than children without the chromosomal deletion (Kates et al., 2001). In addition, parietal gray matter (Eliez et al., 2000) and white matter volumes (Kates et al., 2001; Simon et al., 2005) as well as temporal white matter volumes (Kates et al., 2001) are reduced relative to typically developing controls. These reductions in parietal white matter volumes (15-23%) are disproportionate to the total brain volume reduction (Kates et al., 2001). Although semi-automated measurement methods have revealed that frontal gray and white volumes are disproportionately increased in VCFS and equal to control participants (Eliez et al., 2000; Kates et al., 2001), manual measurement of the frontal lobe volumes suggests that frontal white matter may also be reduced disproportionately to whole brain volume (Kates et al., 2004).

VCFS has been proposed as a prototypical NLD syndrome (Rourke et al., 2002) and visuospatial/perceptual deficits are a phenotypic cognitive trait (Swillen et al., 1999). Parietal lobe structural and functional abnormalities are associated with diminished visuospatial/perceptual functioning in the non-VCFS population (Friedrich, Egly, Rafal, & Beck, 1998; Pesenti, Thioux, Seron, & De Volder, 2000; Warrington & James, 1988). All of the above suggests that investigating the association between parietal lobe morphology and performance on tests of visuospatial perception in children with VCFS would contribute to our understanding of brain – behavior relations in this disorder. We have chosen the Rey-Osterrieth Complex Figure (ROCF; Rey, 1941) to achieve this aim.

### Rey-Osterrieth Complex Figure

The ROCF has been used in both the neuropsychological clinical and research domains, with both adults and children. Within the extant pediatric literature, the ROCF has been utilized as a measure of visuospatial perception, learning and memory (Baron, 2000) in research with

several populations including typically developing youth (Beebe, Ris, Brown, & Dietrich, 2004), epilepsy (Hernandez et al., 2003), phenylketonuria (Antshel & Waisbren, 2003), preterm children (Waber & McCormick, 1995), learning disabilities (Kirkwood et al., 2001) and ADHD (Sami, Carte, Hinshaw, & Zupan, 2003; Seidman et al., 1995). All of these studies found the ROCF to be a sensitive measure to the cognitive difficulties of the identified clinical group.

A previous pediatric research project utilized the ROCF to analyze brain-behavior relationships. Sowell and colleagues (2001) assessed frontal and medial temporal lobe gray matter volume and learning/memory using the ROCF in a sample of 35 youth ages 7 – 16. Results demonstrated that frontal and medial temporal lobe gray matter volumes were associated ( $r = -.5$ ) with delayed visuospatial memory.

In adults, ROCF performance differs as a function of lateralized brain damage; left hemisphere damage affects performance on the parts/details while right hemisphere damage affects performance on the overall gestalt (Poreh & Shye, 1998). This is consistent with the global/local processing theory which states that left hemisphere mechanisms are responsible for attending to the parts, details, and discrete elements of complex visuospatial materials and right hemisphere mechanisms are responsible for attending to the overall gestalt (Delis, Robertson, & Efron, 1986; Fink et al., 1996). In samples of adults with lateralized temporal lobe epilepsy, others (Loring, Lee, & Meador, 1988; Piquet et al., 1994) have suggested that right temporal lobe lesions are associated with ROCF distortion and misplacement recall errors. Barr et al. (1997), however, did not report any recall performance differences between participants with left and right temporal lobe epilepsy. More research is needed to further understand the processes that are involved in ROCF performance.

### Importance of Current Project/Hypotheses

Despite the emerging literature addressing brain - behavior relations in VCFS, no research has specifically utilized the ROCF in children with this disorder as a measure of visuospatial perception, learning and memory. Given the previous research that has identified visuospatial deficits as a primary cognitive phenotypic trait in VCFS, we sought to utilize a measure that has been used in other pediatric populations as an assessment tool for these cognitive functions. In addition, following the lead of Sowell et al. (2001) in their research on typically developing children, we were interested in determining how ROCF performance may be associated with neuroimaging variables in children with developmental delays.

This investigation was designed to examine potential differences in brain-behavior relationships between children with VCFS and control participants. Nonetheless, the previous VCFS and pediatric neuropsychology literatures did not provide any clear indication about the nature of these differences. For this reason, group differences in hypotheses 2 – 4 were explored within a null hypothesis framework. Our *a priori* hypotheses were:

1. Based upon the literature, we hypothesized that children with VCFS will have smaller whole brain volumes than control participants. In addition, after controlling for whole brain volume, parietal lobe gray matter and white matter as well as temporal lobe white matter volumes will be reduced in children with VCFS relative to control participants. Frontal lobe gray and white matter volumes will be relatively preserved in VCFS and will not differ from control participants after controlling for whole brain volume.
2. Volumetric MRI studies will demonstrate a positive association between performance on the ROCF Copy trial and frontal and parietal lobe gray and white matter volumes in the combined control and VCFS sample.

3. Volumetric MRI studies will demonstrate a positive association between performance on the ROCF Recall trials and temporal lobe gray and white matter volumes, but not frontal and parietal lobe gray and white matter volumes, in the combined control and VCFS sample.
4. In the combined control and VCFS sample, left hemisphere (temporal, frontal and parietal) gray and white matter volume will be positively associated with the ROCF – Incidental Elements (internal details) raw score and right hemisphere gray and white matter volume will be positively associated with the ROCF – Structural Elements (base rectangle and main substructures) raw score.

## Methods

### Participants

Children between the ages of 9 and 14 years, 11 months were included in the current project. Ninety-two children with VCFS (*Mean Age* = 11.0 years, *SD* = 2.6 years) and a control group selected to ensure overall comparability on certain demographic variables (e.g., age, race, gender-ratio matched) comprised our study population. Our control group was a sample of 59 community control youth (*Mean Age* = 10.4, *SD* = 2.6). Please see Table 1 for complete participant information.

Children with VCFS were recruited from the ongoing longitudinal study of childhood risk factors for psychosis being conducted at the State University of New York - Upstate Medical University. Families who have a child with VCFS who is actively followed through the Center for the Diagnosis, Treatment, and Study of VCFS at SUNY-Upstate Medical University were informed about the study by the center nurse practitioner. In addition, the study was posted on the VCFS Educational Foundation website. Only children with a Fluorescent In Situ Hybridization (FISH) confirmed deletion in the q11.2 region of chromosome 22 were included in the sample.

Control participants were recruited through the local school system; families of children in elementary and middle school received a flier detailing the study. Children with an identifiable genetic disorder (other than VCFS) and/or children with an identifiable neurological condition (e.g., traumatic brain injury, pre-term birth) that is known to affect cognitive or psychiatric function were excluded from participation. Our control participants did not receive formal molecular genetic screening; VCFS is readily identifiable by a facial phenotype and therefore, a higher level of invasiveness (e.g., DNA analysis) was not indicated for our control participants as a measure of screening for VCFS. All families were provided with paid parking and children received a \$35 gift certificate to a local mall.

### Measures

A large battery of psychological tests was administered in the research protocol. For the current analyses, however, we included only the Wechsler Intelligence Scale for Children – Third edition (WISC-III; Wechsler, 1991) and the ROCF (Rey, 1941).

The first ROCF trial was a copy trial in which the participant was asked to copy a complex figure. The second trial was an immediate recall trial, generally given one minute after the copy trial, in which the participant was asked to recall and draw as much of the figure as possible. Finally, the delayed recall trial, similar in scope to the immediate recall trial, was given 30 minutes later. A sequence of colored pens (as used by Taylor, 1959) was held constant across all participants.

Use of the ROCF in the pediatric realm is complicated by the difficulty of assessing performance in a developmentally sensitive fashion (Bernstein, 1994). Adding to the complexity of assessing a child's performance is that functional similarities between adults and children are known to be subserved by different regions of the brain (Brown et al., 2005; Konrad et al., 2005). In the pediatric domain, a commonly employed instrument to gauge ROCF performance is the Developmental Scoring System (DSS; Bernstein & Waber, 1996). The DSS measures the "Organization", "Style", "Accuracy", and "Errors". Organization score quantifies organizational goodness of complex patterns (Bernstein & Waber, 1996). Style assesses the degree to which the child has the ROCF features aligned correctly and continuously drawn. Accuracy calculates the number of ROCF components copied. Error quantifies how distorted components are, based on rotation, perseveration, misplacement, and conflation of elements.

Age normed MRI volumetric data are not presently available; thus, to permit us to examine age in our statistical models, we employed DSS raw scores. (For some subsequent analyses, however, raw scores were converted to z-scores using norms provided in the DSS manual.). The first author received training and instruction from the DSS authors and scored all ROCF protocols using the DSS. A licensed psychologist or a trained assistant familiar with the DSS double scored all protocols. Scorers were not blind to group assignment.

To enable the use of parametric statistics as well as limit our number of planned analyses, we performed three preliminary sets of analyses on our ROCF data. In the VCFS sample, across all three ROCF trials, DSS Organization and Style raw scores, but not Accuracy and Error raw scores, were positively skewed (Mean skewness = 1.94, SE = .29). Of our 92 children with VCFS, 35 (38%) obtained either the lowest ( $n = 9$ ) or next to lowest possible ( $n = 26$ ) score on both Organization and Style across all three trials. Due to our floor effects, we performed a log transformation on our ROCF Organization and Style raw scores to help normalize the distribution and enable the use of parametric analyses. The log transformation of the DSS Organization and Style scores in the VCFS sample resulted in a more normal distribution (Mean skewness = 0.34, SE = .11).

In light of high intraclass correlations between the DSS measures log Organization and log Style, only log Organization was considered in the analyses. Similarly, because of high intraclass correlations between DSS Accuracy and Errors, only Accuracy scores were included in the analyses. Finally, the high intraclass correlations between the immediate and delayed trials for DSS Organization and Accuracy justified averaging of the two recall scores to form a single recall composite for each of these measures.

Finally, there are a variety of scoring criteria available for the ROCF. Qualitative aspects of ROCF completion are important to consider (Strauss, Sherman, & Spreen, 2006); this is the primary reason that the current analyses focused on the DSS. Although the DSS has been well validated (Bernstein & Waber, 1996), we sought to examine how DSS performance may be related to another commonly employed ROCF scoring algorithm which has been utilized in brain: behavior research (Sowell et al., 2001), the Meyers and Meyers (1995) system.

In our VCFS sample, the associations between DSS Copy Organization, Copy Accuracy and Meyers and Meyers copy scores were  $r = .57$  and  $.96$  respectively. In our control sample, these same associations were  $r = .63$  and  $.98$ . DSS Recall Organization and Copy Accuracy scores in our VCFS sample were equally associated with Meyers and Meyers recall scores,  $r = .65$  and  $.99$ . In our control sample, these same associations were  $r = .67$  and  $.99$ . Thus, DSS scores appear associated with Meyers and Meyers scores.

## Procedures

Informed consent/assent was obtained from parents and children under protocols approved by the institutional review board. Each child enrolled in the study was administered a comprehensive neuropsychological assessment. The ROCF was administered after the halfway break (generally 90 minutes into the assessment). While the children participated in the psychological evaluation, parents completed behavioral rating inventories. Upon completion of the assessment, children received a structural MRI of the brain.

## MRI Acquisition and Image Analysis

Magnetic resonance imaging scans were acquired in the axial plane on a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Best, The Netherlands), utilizing the following T-1 weighted inversion recovery 3-D pulse sequence: TE = 4.6; TR = 20; 2 repetitions; matrix size 256 × 154; FOV 24; multishot = 32; TFE pre IR shortest (394 ms), 1.5 mm slice thickness. Raw, formatted image data were transferred from the MRI scanner to Apple Macintosh Power PC workstations via existing network connections. The image data were imported into the program BrainImage (Reiss, 2002) for removal of non-brain tissue. The isolated brain tissue was subdivided into cerebral lobes, subcortical, brainstem, and cerebellar regions according to a revised Talairach (Talairach & Tournoux, 1988) stereotaxic grid specific for measurement in pediatric study groups (Andreasen et al., 1996; Kaplan et al., 1997; Kates et al., 1999). Each region was then segmented into gray, white, and CSF compartments using an algorithm that assigns voxels to one or more tissue categories based on intensity values and tissue boundaries (Reiss et al., 1998). The segmentation method used was determined reliable for all gray matter, white matter, and CSF volumes (Reiss et al., 1998). Our whole brain volume measure included the CSF compartment. A research assistant (J.P.) who was blind to the diagnosis of each subject performed all measurements.

## Planned Analyses

**Preliminary statistics**—Comparisons on baseline characteristics were first performed using analysis of variance (ANOVA) techniques for continuous variables and chi square tests for categorical variables. As shown in Table 1, IQ differences existed between our VCFS (Mean IQ = 71.7; *SD* = 12.9; Range 40 – 102) and control participants (Mean IQ = 97.1; *SD* = 12.6; Range 71 – 132),  $F(1, 149) = 148.36, p < .001, \eta^2 = .47$ . Thus, we sought to examine how IQ may relate to our two DSS variables in our groups. In our control group, IQ was related to both DSS Copy Organization age corrected z-scores, Spearman rank correlation ( $\rho$ ) = .312,  $p = .019$ , and DSS Recall Organization age corrected z-scores,  $\rho = .413, p = .005$ . However, in our control group, IQ was not associated with either DSS Copy Accuracy age corrected z-scores,  $\rho = .181, p = .203$ , or DSS Recall Accuracy age corrected z-scores,  $\rho = .222, p = .182$ . In our VCFS sample, IQ was not associated with performance on any of the DSS variable age corrected z-scores,  $p < .200, p > .05$ . These analyses suggest that IQ related differently to DSS variables in the VCFS and control groups, thereby precluding the use of IQ as a covariate.

**Hypothesis testing**—To investigate hypothesis 1, we computed a multivariate analysis of covariance (MANCOVA) using whole brain volume as the covariate and lateralized left and right white and gray matter lobar volumes as the dependent measures. Pairwise comparisons of VCFS versus control participants were based on least-squares means adjusted by the Bonferroni method. Eta squared ( $\eta^2$ ) is also reported for all analyses. When  $\eta^2 \geq 0.15$ , effects are considered “large” in magnitude and when  $\eta^2 \geq 0.06$ , effects are viewed as “medium” in magnitude (Cohen, 1988).

Hypotheses 2 and 3 were analyzed using combined sample stepwise regression analyses on each log transformed ROCF copy and recall trial dependent variable. In step 1, age was entered. In step 2, whole brain volume was entered. Thus, age and whole brain volume served as

covariates. In step 3, combined left-right frontal, parietal or temporal lobe gray or white matter volumes were entered, one region at a time. If the variable was not significant it was dropped from the model. Finally, in step 4, the group main effect and the group  $\times$  lobar (frontal, parietal or temporal) volume interaction terms were entered as predictors of log Organization and Accuracy scores on the ROCF copy and recall trials. The stepwise approach was chosen in order to determine the incremental contribution of lobar volumes after controlling for the influence of these other factors. A *t*-test was performed to test the significance of the standardized regression coefficient (beta) for each group of predictor variables as well as each variable within each group to determine whether the contribution of that variable or group of variables was significantly different from zero.

Finally, hypothesis 4 was examined in a fashion comparable to hypotheses two and three, although our outcome variables were raw scores on the DSS Copy Accuracy-Incidental Elements and Structural Elements scales. In addition, left and right hemisphere volumes were regressed onto both of our hypothesis 4 dependent variables to determine if the associations were more robust for one hemisphere versus the other. Our stepwise model included age in step 1 and whole brain volume in step 2. In step 3, left or right hemisphere gray or white matter volumes were entered one at a time. If the variable was not significant it was dropped from the model. In step 4, the group main effect and the group  $\times$  hemisphere volume interaction terms were entered.

## Results

### ROCF Performance

The omnibus MANOVA on the ROCF variables was significant, Wilk's  $\lambda = 0.75$ ,  $F(8, 141) = 14.44$ ,  $p < .001$ ,  $\eta^2 = .57$ . As shown in Table 2, univariate analyses revealed that children with VCFS performed less well across all ROCF variables.

### Hypothesis 1

Relative to control participants (Mean Whole Brain Volume = 1368.2 cm<sup>3</sup>;  $SD = 15.1$ ), children with VCFS (Mean Whole Brain Volume = 1316.4 cm<sup>3</sup>;  $SD = 14.4$ ) had smaller whole brain volume,  $F(1, 149) = 3.21$ ,  $p = .038$ ,  $\eta^2 = .03$ . Thus, whole brain volume was entered as a covariate in examining group differences in lobar volume. Consistent with our hypothesis, after controlling for whole brain volume, the omnibus multivariate analysis of covariance (MANCOVA) was significant, Wilk's  $\lambda = 0.55$ ,  $F(12, 137) = 7.01$ ,  $p < .001$ ,  $\eta^2 = .44$ . As indicated in Table 3, univariate analyses revealed that compared to control participants, children with VCFS had reductions in left parietal gray,  $F(1, 148) = 9.03$ ,  $p = .003$ ,  $\eta^2 = .07$ , and right parietal gray matter volume,  $F(1, 148) = 10.83$ ,  $p < .001$ ,  $\eta^2 = .08$ . After controlling for whole brain volume differences, children with VCFS had increases in left frontal lobe white matter,  $F(1, 148) = 33.24$ ,  $p < .001$ ,  $\eta^2 = .22$ , and right frontal lobe white matter volumes,  $F(1, 148) = 42.57$ ,  $p < .001$ ,  $\eta^2 = .27$ , suggesting disproportionately increased frontal lobes in VCFS. After controlling for whole brain differences, temporal lobe gray and white matter volume differences did not reach significance. In sum, hypothesis one was not strongly supported.

### Hypothesis 2

Regression results are summarized in Table 4 (Copy Organization, Copy Accuracy). As shown in the table, age and whole brain volume were significant predictors of ROCF raw score performance in both models. Even after controlling for these variables, several volumetric variables were significant predictors of ROCF Copy trial performance. As expected, both gray and white matter parietal lobe volumes predicted ROCF Copy Organization raw scores. Our frontal lobe white matter group  $\times$  volume interaction term was also significant, suggesting that

the strength of the associations between frontal lobe white matter volumes and the ROCF Copy Organization raw scores differed between groups. Pearson partial correlation coefficients were calculated to examine the relationships as a function of group. Whole brain volume was partialled out of these analyses. For children with VCFS, frontal lobe white matter volumes were less strongly associated with ROCF Copy Organization raw scores,  $r(91) = -.143, p = .248$ , than in our control group,  $r(58) = .451, p = .009$ .

Significant predictors of ROCF Copy Accuracy trial raw scores were frontal lobe gray and white matter volumes. No group  $\times$  volume interaction terms reached significance.

### Hypothesis 3

Similar to the ROCF Copy trial models, age and whole brain volume predicted ROCF Recall Organization and Accuracy raw scores. After controlling for these variables, frontal lobe gray matter volumes were significant predictors in both models. In the ROCF Recall Organization model, the frontal lobe gray matter group  $\times$  volume interaction term was also significant, suggesting that the strength of the associations between frontal lobe gray matter volumes and the ROCF Recall Organization raw scores differed between groups. Similar to our Copy Organization interactions, Pearson partial correlation coefficients revealed that for children with VCFS, frontal lobe gray matter volumes were less strongly associated with ROCF Recall Organization raw scores,  $r(91) = .180, p = .205$ , than in our control group,  $r(58) = .477, p = .004$ . No group  $\times$  volume interaction terms reached significance in the ROCF Recall Accuracy model. Please see Table 5 for full ROCF recall trial stepwise regression results.

### Hypothesis 4

Similar to our hypotheses two and three regression models, whole brain volume and age were significant predictors of both Incidental Elements and Structural Elements accuracy raw scores. As shown in Table 6, no other variables were significant predictors of ROCF-Copy trial Incidental Elements Accuracy raw scores. In our ROCF-Copy Structural Elements Accuracy raw score model, right hemisphere white matter volume was a significant predictor. In addition, the group  $\times$  volume interaction term was also significant, suggesting that the strength of the associations between volumes and the ROCF-Copy Structural Elements Accuracy raw scores differed between groups. Pearson partial correlation coefficients were calculated to examine the relationships as a function of group. Whole brain volume was partialled out of these analyses. For children with VCFS, right hemisphere white matter volumes were more strongly associated with ROCF-Copy Structural Elements Accuracy raw scores,  $r(91) = .480, p = .008$ , than in our control group,  $r(58) = .153, p = .409$ .

### IQ-matched analyses

To further explore the impact of generalized cognitive delays on our results, we compared a subset of children with VCFS with a FSIQ  $\geq 80$  ( $n = 33$ ) to a subset of control participants with a FSIQ  $\geq 80$  and a FSIQ that was no higher than the maximum FSIQ of the VCFS group (FSIQ=102) ( $n = 35$ ). These two groups did not differ on FSIQ,  $F(1, 66) = 1.03, p = .673, \eta^2 = .02$  or age,  $F(1, 66) = 1.27, p = .524, \eta^2 = .02$ . Nonetheless, ROCF performance differed between the IQ-matched subsamples; across all ROCF outcome variables, children with VCFS performed less well with large effect sizes  $\eta^2 > .30$ .

**Hypothesis one**—Whole brain volume means were equivalent between the IQ-matched subset,  $F(1, 66) = 0.23, p = .655, \eta^2 = .01$ . In the IQ-matched groups, the omnibus MANOVA was significant, Wilk's  $\lambda = 0.50, F(12, 55) = 4.72, p < .001, \eta^2 = .53$ . Univariate analyses suggested identical results compared to the full sample analyses; compared to control participants, children with VCFS had reductions in left parietal gray,  $F(1, 66) = 5.72, p = .020, \eta^2 = .08$ , and right parietal gray matter volume,  $F(1, 66) = 3.93, p = .038, \eta^2 = .06$ . Children

with VCFS had increases in left frontal lobe white matter,  $F(1, 66) = 3.82, p = .040, \eta^2 = .06$ , and right frontal lobe white matter volumes,  $F(1, 66) = 4.80, p = .031, \eta^2 = .07$ .

**Hypothesis two**—In both groups, gray and white matter parietal lobe volumes predicted ROCF Copy Organization raw scores. For children with VCFS, frontal lobe white matter volumes were less strongly associated with ROCF Copy Organization raw scores,  $r(32) = -.109, p = .342$ , than in our control group,  $r(34) = .427, p = .015$ . Significant predictors of ROCF Copy Accuracy trial raw scores were frontal lobe gray and white matter volumes. No group  $\times$  volume interaction terms reached significance. These results are identical to those obtained on the full sample.

**Hypothesis three**—Frontal lobe gray matter volumes were significant predictors in both models. In the ROCF Recall Organization model, the frontal lobe gray matter group  $\times$  volume interaction term was also significant, suggesting that the strength of the associations between frontal lobe gray matter volumes and the ROCF Recall Organization raw scores differed between groups. Similar to our Copy Organization interactions, Pearson partial correlation coefficients revealed that for children with VCFS, frontal lobe gray matter volumes were less strongly associated with ROCF Recall Organization raw scores,  $r(32) = .144, p = .311$ , than in our control group,  $r(34) = .505, p < .001$ . No group  $\times$  volume interaction terms reached significance in the ROCF Recall Accuracy model. These results are identical to those obtained on the full sample.

**Hypothesis four**—Whole brain volume and age were significant predictors of both Incidental Elements and Structural Elements accuracy raw scores. In our ROCF-Copy Structural Elements Accuracy raw score model, right hemisphere white matter volume was a significant predictor. In addition, the group  $\times$  volume interaction term was also significant; Pearson partial correlation coefficients were calculated to examine the relationships as a function of group. For children with VCFS, right hemisphere white matter volumes were more strongly associated with ROCF-Copy Structural Elements Accuracy raw scores,  $r(32) = .511, p < .001$ , than in our control group,  $r(34) = .111, p = .428$ . These results are identical to those obtained on the full sample.

## Discussion

The present study explored brain - behavior relationships in children with VCFS using the ROCF. Our data, as well as the work of others, suggest that age (Akshoomoff & Stiles, 1995) and whole brain volume contributed to ROCF performance on both the Copy and Recall trials. More novel ROCF brain - behavior findings include (a) for both groups, parietal lobe volumes (both gray and white matter) predicted ROCF Copy Organization performance and frontal lobe volumes (both gray and white matter) predicted ROCF Copy Accuracy performance; (b) for control participants, frontal lobe white matter predicted ROCF Copy Organization performance; (c) ROCF Recall Organization performance was best predicted by frontal lobe gray matter volume only in our control participants yet ROCF Recall Accuracy performance was best predicted by frontal lobe gray matter volume in both groups; (d) in children with VCFS, performance on the ROCF Copy Structural Elements Accuracy scale was best predicted by right hemisphere white matter volume; and (e) unexpectedly, temporal lobe was not predictive of any performance measures on the ROCF.

Mirroring the work of others, our data also suggest that compared to control participants, children with VCFS: (a) perform less well on all aspects of the ROCF; (b) have lower whole brain volume; (c) exhibit reductions in parietal lobe gray and white matter bilaterally, disproportionate to whole brain volume; (d) exhibit increased volumes of frontal lobe white

matter bilaterally, disproportionate to whole brain volume; and (e) exhibit preserved temporal lobe volumes.

As has been noted previously, children with VCFS have difficulty on visuospatial tasks, and task performance has been hypothesized to be associated with anomalous posterior parietal lobe functioning (Simon et al., 2005). In both controls and VCFS participants, our data support the involvement of parietal gray and white matter mechanisms in ROCF Copy performance. One central function of the parietal lobes is integrative and mediating interactions between spatial orienting and higher-level, more abstract, cognitive functions (Andersen, 1997; Huk & Shadlen, 2005; Oristaglio et al., 2006; Quintana & Fuster, 1993). Although both groups of children demonstrated associations between ROCF Copy and parietal volumes, typically developing children also demonstrated an association between ROCF Copy and frontal lobe white matter volumes. A central function of the frontal lobes is executive and supervisory, serving to monitor and check performance over time (Fuster, 1991; Goldman-Rakic, 1996; Stuss et al., 1995). This suggests that for the VCFS children, ROCF Copy deficits may be due to difficulties in cognitive integration, whereas for typically developing children, variability in ROCF Copy performance may be related to both cognitive integration as well as the more executive components of the task.

Both our VCFS and control data suggest that gray matter frontal lobe is also associated with visuoconstruction abilities. In both samples, yet stronger in control participants, frontal lobe gray matter volume was also associated with recall performance. ROCF recall performance taps retrieval skills, which are partially subserved by the frontal lobe (Waber, Bernstein & Merola, 1989). Accordingly, variability in frontal-mediated retrieval skills appears to be contributing to recall performance in children with VCFS. In addition, the ROCF requires that visuospatial information be not only analyzed, but also relayed to output systems and controlled by these same systems. Theoretically, these processes require communication between parietal spatial information centers and frontal lobes. Children with VCFS exhibited a loss of normal structure-function associations with respect to the frontal lobe's role in cognitive organization. Our recent functional neuroimaging working memory study similarly showed youth with VCFS to have frontal hypoactivation (Kates et al., 2007). This further supports the notion that structural / volumetric preservation of the frontal lobe in VCFS does not imply preserved functioning.

VCFS is a neurodevelopmental disorder that largely (~90%) results from *de novo* deletions and the DNA rearrangement that caused the deletion usually has happened during gametogenesis of the mother's egg or father's sperm. Having such an early brain insult likely alters functional brain organization, and skills localized in adults, may be more widely diffused in the atypically developing brain (Ewing-Cobbs, Barnes, & Fletcher, 2003). This may explain why children with VCFS exhibited a loss of normal frontal lobe structure-function associations for cognitive organization.

The medial temporal lobe area, including the hippocampus, has traditionally been regarded as one of the cerebral areas more central to memory (Eichenbaum, 2000; Squire, 1983). Nonetheless, we failed to find an association between temporal lobe volume and ROCF recall performance. We measured total temporal lobe volume here; accordingly, our measures may have been too global to reflect the frequently reported association between medial temporal lobe regions and memory. Instead of temporal lobe volume associations with ROCF recall performance, our data suggest that the frontal lobe may be more central to ROCF recall performance in children. Others (Sowell et al., 2001) have similarly reported that frontal lobe volume is associated with ROCF recall performance in children.

Another possible explanation for these findings is that there are a variety of mechanisms and strategies that can be employed to guide ROCF performance. First, although the ROCF is a measure of visuospatial perception, learning and memory, performance is likely to involve other subskills as well (e.g., fine motor control likely makes a contribution). Thus, ROCF performance may be affected by not only regions central to the purported ability (e.g., temporal lobe and memory) but others as well. Second, it is also possible that the ROCF can be performed with a number of strategies, including verbal mediation. Given that frontoparietal mechanisms are strongly implicated in verbal working memory (Cabeza & Nyberg, 2000), it may be that verbal mediation is also making a contribution towards ROCF recall performance.

Finally, our VCFS data are consistent with other pediatric research reporting associations between ROCF configurational/incidental element accuracy and cerebral lateralization (Akshoomoff et al., 2002). In their study, Akshoomoff et al. reported albeit minor differences suggestive of a double dissociation; children with left hemisphere damage performed less well on the incidental elements and children with right hemisphere damage performed less well on the configurational elements.

The associations between right hemisphere volumetric data and performance on the ROCF “configurational” aspects only emerged in our VCFS sample. Why this did not occur in our control sample is presently unclear but may be related to the neurological deficits associated with VCFS. For example, typically developing children may be able to utilize a variety of alternative strategies subserved by different brain regions to meet task demands. Children with neurological dysfunction, like children with VCFS, may not have these alternative strategies available.

### Limitations & Future Directions

Although the focus of the current project was on visuospatial and memory abilities, it is essential to bear in mind that many of the children with VCFS have more pervasive cognitive deficits than simply visuospatial, constructional or memory skills alone. Although our data and the work of others (Simon et al., 2005) suggest that visuospatial skills may be disproportionately impaired against a background of more generalized cognitive delay, it is still important to bear in mind that the tasks used to study psychological phenomena are often affected by multiple psychological processes (Knight & Silverstein, 2001). Thus, performance impairments on the ROCF may reflect differential test psychometric properties for children with generalized delays rather than a *specific* cognitive deficit (Chapman & Chapman, 1978).

We did not assess all of the potentially relevant factors predictive of ROCF performance. Instead, our focus was on a subset of potential risk factors that we attempted to assess as thoroughly and rigorously as possible. Multivariate analyses examining an even broader set of variables would be informative. Specifically, the inclusion of previous experience with visuospatial tasks may be particularly valuable. In addition, both the use of a single measure to investigate relationships between brain structure and function as well as our choice of the DSS both suggest that our findings should be considered preliminary until other groups can replicate these results using more comprehensive batteries and other ROCF scoring algorithms.

The present study utilized MRI; the use of other imaging technologies in children with VCFS appears to be a logical next step. In light of the white matter alterations noted in our data, diffusion tensor imaging may be an appropriate technology to consider in VCFS research. In addition, the loss of an expected structure – function association between frontal lobe volumes and perceptual organization suggests that functional imaging studies would also be very informative. These are currently underway in our laboratory.

Associations between MRI and ROCF have been inconsistent in the past with some studies reporting negative relationships (Sowell et al., 2001). This inconsistency may be a function of the varying ages of the participants included in different studies, the scoring system used for quantifying ROCF performance or some combination of both. For example, Sowell et al. studied children ages 7 – 16, a time when significant neural reorganization and pruning are occurring. These investigators also employed a different ROCF performance measure. Future research should continue to assess the relationships between MRI and ROCF variables.

## Conclusions

Despite these limitations, our data indicate that children with VCFS have functionally as well as structurally different brains relative to typically developing children. Identical results were also obtained in IQ-matched and whole brain volume-matched subsamples. Our findings suggest that we may not be able to make the same assumptions about the organization of, and the localization of, the brain structures that subserve specific cognitive functions in the abnormally developing brain as can be made in the typically developing brain.

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**Table 1**  
**Background Information**

Variable	VCFS ( <i>n</i> = 92)	Control ( <i>n</i> = 59)
Age	11.0 (2.6)	10.4 (2.6)
Ethnicity (% Caucasian)	93	93
Gender (% girls)	45	43
Socioeconomic status <sup>a</sup>	49.3 (11.7) *	42.6 (13.7)
WISC – III Full Scale IQ	71.7 (12.9) ***	97.1 (12.6)

*Note.* WISC-III = Wechsler Intelligence Scale for Children – 3<sup>rd</sup> edition (Wechsler, 1991).

<sup>a</sup>Socioeconomic status measured by Hollingshead (1975) scale.

\*  $p < .05$ .

**Table 2**  
**Rey-Osterrieth Complex Figure Performance**

Test	VCFS	Control	F (1, 149)	$\eta^2$
ROCF Copy Organization <sup>a</sup>	- 1.3 (0.8)	0.2 (0.1)	11.43 ***	.16
ROCF Immediate Recall Organization	- 1.2 (0.9)	- 0.2 (0.2)	9.21 ***	.11
ROCF Delayed Recall Organization	- 1.1 (0.7)	- 0.1 (0.1)	8.03 ***	.10
ROCF Copy Structural Element Accuracy	- 1.9 (0.9)	0.6 (0.2)	13.13 ***	.19
ROCF Immediate Recall Structural Element Accuracy	- 1.6 (0.8)	0.4 (0.1)	10.68 ***	.14
ROCF Delayed Recall Structural Element Accuracy	- 1.6 (0.7)	0.5 (0.4)	11.71 ***	.15
ROCF Copy Incidental Element Accuracy	- 1.0 (0.3)	0.1 (0.3)	7.39 ***	.09
ROCF Immediate Recall Incidental Element Accuracy	- 0.8 (0.3)	- 0.1 (0.2)	7.01 ***	.08
ROCF Delayed Recall Incidental Element Accuracy	- 0.8 (0.3)	- 0.1 (0.2)	6.98 ***	.07

Note. ROCF = Rey-Osterrieth Complex Figure (Rey, 1941).

<sup>a</sup> Scored using the Developmental Scoring System (Bernstein & Waber, 1996); scores are presented as z-scores based upon normative data.

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 $p < .001$ .

**Table 3**  
**Volumetric MRI Data Corrected for Whole Brain Volume**

Brain Region of Interest	VCFS	Control	F (1, 149)	$\eta^2$
Left Frontal Lobe Gray Matter volume <sup>a</sup>	117.6 (11.7)	117.4 (12.7)	3.70	.03
Right Frontal Lobe Gray Matter volume	120.9 (12.2)	122.2 (13.4)	0.97	.01
Left Frontal Lobe White Matter volume	75.7 (11.7)	70.0 (10.6)	33.24 ***	.22
Right Frontal Lobe White Matter volume	77.9 (12.5)	71.6 (10.7)	42.57 ***	.27
Left Parietal Lobe Gray Matter volume	75.1 (7.8)	79.7 (9.6)	9.03 **	.07
Right Parietal Lobe Gray Matter volume	75.1 (7.3)	79.7 (9.8)	10.83 ***	.08
Left Parietal Lobe White Matter volume	51.2 (8.3)	52.2 (7.3)	0.97	.01
Right Parietal Lobe White Matter volume	52.2 (8.3)	53.3 (7.3)	0.76	.01
Left Temporal Lobe Gray Matter volume	69.8 (7.4)	71.5 (7.8)	0.01	.01
Right Temporal Lobe Gray Matter volume	69.6 (7.2)	72.6 (7.7)	2.44	.02
Left Temporal Lobe White Matter volume	29.0 (4.8)	29.2 (4.8)	1.40	.01
Right Temporal Lobe White Matter volume	28.5 (4.7)	28.8 (5.1)	1.65	.01

Note.

<sup>a</sup>Measurement unit is cubic centimeters (cm<sup>3</sup>).

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 $p < .01$ ;

\*\*\*  
 $p < .001$ .

**Table 4**  
**Stepwise Regression Analyses for ROCF Copy Trial**

	Total R <sup>2</sup>	$\beta^*$	<i>t</i>	<i>p</i> -value
<i>Copy Organization</i>	.53			
Age		.396	4.03	.001
Whole Brain Volume		.218	2.75	.012
Frontal Lobe Gray Matter volume		.014	0.86	.645
Group × Volume Interaction		.080	1.04	.341
Frontal Lobe White Matter volume		.181	1.49	.083
Group × Volume Interaction		.276	3.63	.017
Parietal Lobe Gray Matter volume		.214	2.87	.019
Group × Volume Interaction		.103	1.32	.258
Parietal Lobe White Matter volume		.208	2.64	.008
Group × Volume Interaction		.011	0.65	.688
Temporal Lobe Gray Matter volume		-.054	0.78	.503
Group × Volume Interaction		.007	0.09	.913
Temporal Lobe White Matter volume		.042	0.45	.545
Group × Volume Interaction		.018	0.23	.704
<i>Copy Accuracy</i>	.41			
Age		.313	2.78	.011
Whole Brain Volume		.201	2.42	.023
Frontal Lobe Gray Matter volume		.188	1.65	.043
Group × Volume Interaction		.054	0.45	.525
Frontal Lobe White Matter volume		.212	1.80	.018
Group × Volume Interaction		.087	0.43	.646
Parietal Lobe Gray Matter volume		.098	1.00	.408
Group × Volume Interaction		.038	0.16	.703
Parietal Lobe White Matter volume		.083	1.03	.462
Group × Volume Interaction		.048	0.41	.745
Temporal Lobe Gray Matter volume		.013	0.18	.778
Group × Volume Interaction		.009	0.11	.881
Temporal Lobe White Matter volume		.045	0.32	.769
Group × Volume Interaction		.041	0.28	.777

Note. Rey-Osterrieth Complex Figure – DSS (Bernstein & Waber, 1996) raw scores used in analyses.

\* Standardized regression coefficients.

**Table 5**  
**Stepwise Regression Analyses for ROCF Recall Trials**

	Total R <sup>2</sup>	$\beta^*$	<i>t</i>	<i>p</i> -value
<i>Recall Organization</i>	.58			
Age		.402	4.45	.001
Whole Brain Volume		.199	2.24	.033
Frontal Lobe Gray Matter volume		.231	2.56	.009
Group × Volume Interaction		.313	2.95	.001
Frontal Lobe White Matter volume		.108	0.67	.303
Group × Volume Interaction		.102	0.55	.290
Parietal Lobe Gray Matter volume		.019	0.32	.769
Group × Volume Interaction		.202	1.96	.089
Parietal Lobe White Matter volume		.032	0.11	.882
Group × Volume Interaction		.012	0.31	.863
Temporal Lobe Gray Matter volume		.032	0.19	.647
Group × Volume Interaction		.041	0.11	.750
Temporal Lobe White Matter volume		.004	0.08	.919
Group × Volume Interaction		.019	0.22	.888
<i>Recall Accuracy</i>	.55			
Age		.285	2.11	.040
Whole Brain Volume		.188	1.75	.051
Frontal Lobe Gray Matter volume		.234	1.86	.044
Group × Volume Interaction		.018	0.11	.807
Frontal Lobe White Matter volume		.141	0.63	.549
Group × Volume Interaction		.065	0.36	.703
Parietal Lobe Gray Matter volume		.053	0.24	.756
Group × Volume Interaction		.009	0.05	.892
Parietal Lobe White Matter volume		.034	0.22	.705
Group × Volume Interaction		.054	0.50	.803
Temporal Lobe Gray Matter volume		.032	0.27	.801
Group × Volume Interaction		.031	0.22	.790
Temporal Lobe White Matter volume		.081	0.59	.634
Group × Volume Interaction		.058	0.44	.619

Note. Rey-Osterrieth Complex Figure – DSS (Bernstein & Waber, 1996) raw scores used in analyses.

\* Standardized regression coefficients.

**Table 6**  
**Stepwise Regression Analyses for ROCF Copy Accuracy**

	Total R <sup>2</sup>	$\beta^*$	<i>t</i>	<i>p</i> -value
<i>Incidental Elements</i>	.48			
Age		.530	5.65	.001
Whole Brain Volume		.214	2.98	.001
Left Hemisphere Gray Matter volume		.102	0.83	.355
Group $\times$ Volume Interaction		.081	0.43	.636
Left Hemisphere White Matter volume		.174	1.54	.106
Group $\times$ Volume Interaction		.007	0.02	.909
Right Hemisphere Gray Matter volume		.042	0.20	.847
Group $\times$ Volume Interaction		.009	0.01	.917
Right Hemisphere White Matter volume		.032	0.27	.793
Group $\times$ Volume Interaction		.053	0.31	.886
<i>Structural Elements</i>	.62			
Age		.563	5.76	.001
Whole Brain Volume		.310	3.32	.001
Left Hemisphere Gray Matter volume		.067	0.28	.757
Group $\times$ Volume Interaction		.033	0.20	.792
Left Hemisphere White Matter volume		.065	0.29	.674
Group $\times$ Volume Interaction		.064	0.30	.646
Right Hemisphere Gray Matter volume		.076	0.59	.418
Group $\times$ Volume Interaction		.087	0.67	.781
Right Hemisphere White Matter volume		.388	3.07	.001
Group $\times$ Volume Interaction		.370	2.97	.001

*Note.* Rey-Osterrieth Complex Figure – DSS (Bernstein & Waber, 1996) raw scores used in analyses.

\* Standardized regression coefficients.