

Research Report

Arithmetic ability and parietal alterations: A diffusion tensor imaging study in Velocardiofacial syndrome

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Abstract

Velocardiofacial syndrome (VCFS) is a congenital anomaly that causes somatic as well as cognitive and psychiatric impairments. Previous studies have found specific deficits in arithmetic abilities in subjects with VCFS. In this study, we investigated whether abnormalities in white matter pathways are correlated with reduced arithmetic ability. Nineteen individuals with VCFS aged 7–19 years received diffusion-weighted magnetic resonance imaging (MRI) scans. A linear regression model was used to correlate fractional anisotropy (FA) values with scores of the arithmetic subscale on the WISC/WAIS on a voxel-by-voxel basis, after covarying for any IQ- and age-related effects. There was a statistically significant positive correlation between the arithmetic score on the WISC/WAIS and FA values in white matter tracts adjacent to the left supramarginal and angular gyri, as well as along the left intraparietal sulcus. Inferior parietal lobe white matter structural aberrations may contribute to reduced arithmetic ability in VCFS.

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1. Introduction

Velocardiofacial syndrome (VCFS), a genetic syndrome resulting from a deletion in 22q11.2, affects 1 in 3000–5000 individuals [39,52]. Major features of VCFS include facial and cardiac anomalies, developmental delay, cognitive disability, and psychiatric disorders. Children and adolescents with VCFS demonstrate an uneven cognitive profile, with several nonverbal skills being more impaired than verbal abilities [5,20,26,35,50,57]. For example, particular deficits in non-verbal processing, visual–spatial skills, and mathematics were observed in a study of 81 children and

adolescents with 22q11.2 deletion who completed the Wechsler Individual Achievement Test [57].

Neuropsychological, lesion, and neuroimaging studies in humans and primates have repeatedly demonstrated that a neural network comprising prefrontal, posterior parietal, and cingulate regions is involved in mathematical reasoning [8,11,13,27,28,37,38,40,45,47]. The neural substrate of arithmetic dysfunction in VCFS is not yet understood, however, there is evidence suggesting that the 22q11.2 deletion affects the structure of parietal and frontal regions and the function of posterior parietal regions. Specifically, volumetric magnetic resonance imaging (MRI) studies in VCFS demonstrate both gray and white matter volume reduction in parietal lobes [15,24]. Using semi-automated techniques to measure brain volume, total volume of frontal brain regions was found to be preserved in VCFS

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[15,24,25]; however, a recent preliminary study manually measured frontal brain regions in VCFS and found a proportional decrease in frontal total brain volume [25]. Frontal white matter volume was reduced beyond the reduction in frontal total brain volume [25]. In another study, adults with VCFS demonstrated reduced white matter density in frontal and parietal regions [1].

Reduced total cerebellar volume and cerebellar gray matter volume also were reported in adults with VCFS [53]. The cerebellum is known to play an important role in cognitive processes, such as working memory [7,21], which are engaged during the performance of mental arithmetic tasks. Finally, a functional MRI (fMRI) study investigating arithmetic performance in VCFS found an abnormal pattern of brain activation in the left supramarginal gyrus related to increased task difficulty [16].

We recently investigated white matter tracts in VCFS using diffusion tensor imaging (DTI) and found that subjects with VCFS have reduced white matter anisotropy in prefrontal and posterior parietal regions [2]. We hypothesized that impaired white matter circuitry in these areas may contribute to arithmetic disability in individuals with VCFS. In the present study, we investigated the correlation between arithmetic performance in young subjects with VCFS and white matter tract anisotropy. We predicted that reduced white matter anisotropy in prefrontal–parietal networks would be associated with reduced arithmetic performance.

2. Materials and methods

2.1. Subjects

Participants included 13 male and 6 female subjects with VCFS, aged 7.2 to 19.7 years (mean age = 12.2 ± 3.9 years). Only individuals with the 22q11.2 micro-deletion, as confirmed by fluorescent in-situ hybridization (FISH), were included in the study. After describing the study protocol to all participating subjects and their parents, we obtained written informed consent as approved by the institutional review board of Stanford University. In order to compare our sample with typically developing individuals, we also used a control group consisting of 19 typically developing subjects individually matched for age and gender to the VCFS group (control mean age = 14.4 ± 4.2 years). The mean age difference was not significant between groups ($t = 1.48$; $P \leq 0.1461$).

2.2. Cognitive assessment

Participants were given the Wechsler Intelligence Scale for Children—Third Edition (WISC-III; ages 6–17) or the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; ages 17 and over) [54,55]. Mean IQ for the VCFS group was 70 ± 13.5 ; range = 42–90, and for the control group

mean IQ was 117.5 ± 8.9 ; range = 103–132. The arithmetic subscales of the WISC and the WAIS were used as determinants of arithmetic ability. Arithmetic scores for the VCFS group ranged between 1 and 9, mean = 4.89 ± 2.66 . In the control group, arithmetic scores ranged between 7 and 18, mean = 13.1 ± 3.5 . There were no gender differences in arithmetic performance ($t = 0.066$; $P \leq 0.94$). The arithmetic subtests of the WAIS-III and the WISC-III measure numerical reasoning and the ability to solve arithmetic problems [44].

2.3. MRI

Magnetic resonance images were acquired using a GE-Signa 1.5 T scanner (General Electric; Milwaukee). A diffusion-weighted sequence was based on a single-shot spin-echo echo-planar imaging sequence with diffusion sensitizing gradients (field of view = 24 cm, matrix size = 128×128 zero filled to 256×256 , TE/TR = 106/6000 ms, 19/18 axial-oblique slices, slice thickness 5 mm/skip 1 mm), excluding the cerebellum and the brainstem. Diffusion gradient duration was $\delta = 32$ ms, diffusion weighting was $b = 900$ s/mm². In addition, two reference measurements (b_0 -scans) were performed and averaged for each slice, with the diffusion-encoding gradients turned off.

Diffusion was measured along six non-collinear directions: XY , XZ , YZ , $-XY$, $-XZ$, and $-YZ$. This pattern was repeated four times for each slice with the sign of all diffusion gradients inverted for odd repetitions.

Diffusion tensor information [4] was processed on a per-pixel basis after the raw images were spatially corrected for eddy-current-induced distortions [9].

2.4. Image processing

In this study, standardized scores on the “arithmetic” subtest of the WISC-III (ages 6 to 16 years) or WAIS-III (17 years and older) were correlated with the fractional anisotropy (FA) values of each voxel. Fractional anisotropy is an intravoxel measure that yields values between 0 (perfectly isotropic diffusion) and 1 (perfectly anisotropic diffusion). The degree of anisotropy in a voxel is determined by microstructural features of the tissue in that particular voxel, including fiber diameter and density, degree of myelination, and macrostructural features such as intravoxel fiber-tract coherence. Greater anisotropy within a measured voxel corresponds to a higher FA value.

The FA was calculated for each voxel according to Basser and Pierpaoli [4] to produce a fractional anisotropy image. The FA images were further processed using Statistical Parametric Mapping software (SPM99; Wellcome, UK). The T2-weighted image map was used to determine normalizing parameters subsequently applied to the FA images using SPM99. Re-sampling in the normalization process eliminates potential differences due to different

matrix sizes. The normalized FA images were smoothed with a 4 mm kernel to increase the signal-to-noise ratio. Subsequently, VCFS and control subjects were analyzed separately using a linear regression model to correlate the FA maps with subject's WISC or WAIS arithmetic subscale, on a voxel-by-voxel basis. Full-scale IQ and age were factored in as nuisance covariates. Age was included in this analysis due to evidence of white matter changes with age throughout childhood and adolescence [3,46]. Finally, the joint expected probability distribution of the height and extent of Z-scores, with height ($Z > 2.33$; $P < 0.01$) and extent ($P < 0.05$) thresholds, was used to determine the presence of significant clusters of difference and correct for spatial correlation in the data. A white matter mask was constructed using the average of high-resolution normalized SPGR images of all subjects. This mask was used to highlight changes in white matter tracts by eliminating noise and edge effects (Table 1).

A post-hoc confirmatory analysis was conducted in the VCFS group using the cluster that showed significant correlation between FA values and arithmetic scores as regions of interest (ROIs). The average FA value within the ROIs was computed and subsequently correlated with a residual variable based on the simple linear regression of arithmetic score, IQ, and age, thereby removing the variance in arithmetic score explained by IQ and age. FA values were normally distributed, and a parametric test (Pearson correlation) was used to examine FA–arithmetic score correlations.

3. Results

Subjects with VCFS showed a significant correlation in left parietal areas, between the arithmetic subtest score and FA values, after covarying for full-scale IQ scores and age (Fig. 1). Specifically, a cluster representing a significant positive correlation was observed in white matter (1) along the left intraparietal sulcus, (2) within the left angular gyrus, and (3) approaching the left supramarginal gyrus.

An additional cluster was observed bordering the right supramarginal gyrus and the right angular gyrus. However, this cluster merely approached significance ($P = 0.08$).

Table 1

Voxel coordinates in Talairach space and the associated Z-scores for the most significant voxel in the statistical parametric map in which FA values were significantly correlated with the WISC/WAIS arithmetic scores

Location of significant FA differences	Cluster size in voxels	Talairach coordinates of most significant voxel	Z-score
Left intraparietal sulcus and angular gyrus, extending into the supramarginal gyrus	212	−28, −62, 30	4.05

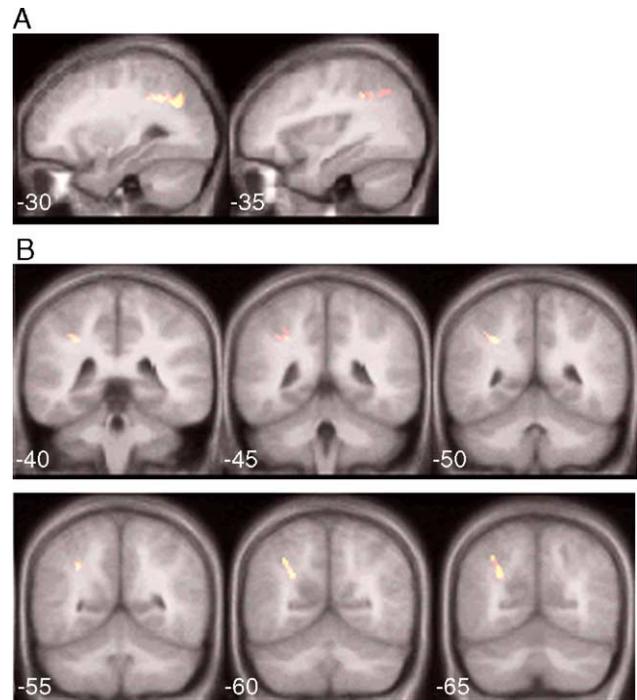


Fig. 1. Voxels that showed significant correlation between FA values and the WISC/WAIS arithmetic subscale score. (A) Sagittal view. (B) Coronal view.

Examination of the correlation between FA values and arithmetic scores by ROI analysis confirmed the significant FA values–arithmetic scores correlation observed in the voxel-based whole brain analyses (Fig. 2). There was a significant correlation between FA and the residual variable (calculated for the WISC/WAIS arithmetic subtest score, IQ scores, and age) in the left inferior parietal cluster ($R = 0.8$; $P < 0.0001$).

In the control group, there was no significant correlation between white matter anisotropy and arithmetic scores in inferior parietal regions. However, there was a significant correlation between white matter anisotropy and arithmetic scores in the right centrum semiovale in the fronto-parietal region, as well as in the splenium of the corpus callosum extending into the right occipital lobe.

4. Discussion

In this study, we observed a significant correlation between white matter anisotropy in inferior parietal regions and arithmetic performance in young individuals with VCFS. This correlation was unique to individuals with VCFS and was not observed in typically developing individuals.

These findings complement results from previous imaging studies, where structural and functional abnormalities in parietal regions were observed in VCFS. At the gross morphological level, the 22q11.2 deletion appears to affect white matter to a greater extent than gray matter [1,15,24,25,53]. Specifically, prominent reductions in white

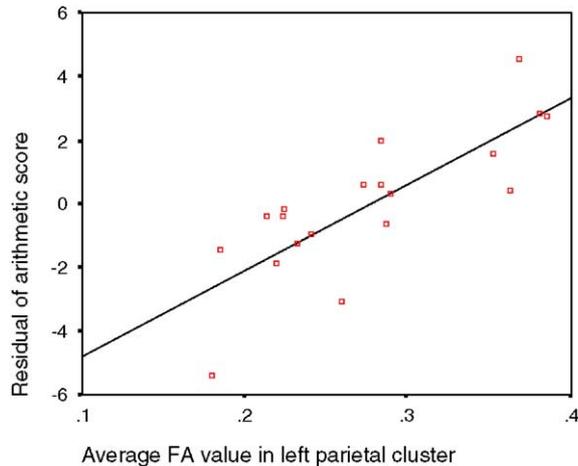


Fig. 2. A correlation graph between the average FA value in the left parietal cluster described in Table 1 and the residual arithmetic subtest score after removing the influence of FSIQ and age.

matter volume, particularly in parietal and prefrontal brain regions, were observed in several volumetric MRI studies of children, adolescents, and adults with the 22q11.2 deletion [1,15,24,25]. The study reported here is the first to suggest that impairment of white matter pathways in posterior parietal regions may contribute to impaired arithmetic performance in VCFS.

A distributed network involved in arithmetic abilities that includes prefrontal and posterior parietal regions has been repeatedly demonstrated in control subjects and in patients with cerebral lesions using neuropsychological and functional neuroimaging techniques [6,32,49,56]. Activation in the inferior parietal cortex has been specifically linked to arithmetic complexity [31]. Furthermore, this is the only region activated during simple arithmetic tasks [14,36,41], whereas activation in prefrontal regions varies with requirements for rapid processing [32]. Taken together, these findings suggest that parietal regions play a direct role in numeric processing, while frontal regions participate in the working memory aspects of complex computations.

Within the parietal lobe, the inferior parietal lobule – comprised of the intraparietal sulcus, the angular gyrus, and the supramarginal gyrus – has been repeatedly linked to arithmetic reasoning. Gerstmann syndrome, involving acalculia, is classically mapped to inferior parietal structures [10,18,43]. More specifically, lesion, electrostimulation, and imaging studies have demonstrated the importance of the intraparietal sulcus [12,14,41,47], the angular gyrus [13,19,29,31,32,43], and the supramarginal gyrus [43] in arithmetic processing. Although the specific contributions of parietal lobe subregions are still under investigation, our study provides evidence linking inferior parietal white matter tract abnormalities to impaired numerical processing in individuals with VCFS.

In our analysis, we did not find support for our hypothesis that aberrations in prefrontal white matter

structure would be correlated with reduced arithmetic ability. One possible explanation for lack of prefrontal findings is that prefrontal pathways and pathways connecting prefrontal and parietal regions are affected to a lesser degree than parietal pathways in VCFS. To test this hypothesis, we repeated our analysis with a lower threshold for defining cluster significance (height: $Z > 1.67$; $P < 0.05$). Extent ($P < 0.05$) threshold was unchanged. In this less stringent analysis, we did find significant correlation between FA values and arithmetic scores in white matter between frontal and parietal regions, however, there were no significant clusters within prefrontal regions. These findings suggest that, although prefrontal and parietal regions are important for arithmetic processing, the pathways affected by VCFS involve only parietal and perhaps fronto-parietal pathways. Impaired white matter structure in parietal regions may be sufficient to explain difficulties in arithmetic ability observed in VCFS as this impairment may hinder integration of information between parietal areas and other brain regions, including the prefrontal cortex. Our findings complement the previous fMRI study in VCFS that investigated the relationship between brain function and mathematical performance in VCFS and found an abnormal activation pattern in parietal areas but not in prefrontal areas [16].

Beyond deficits in arithmetic performance, these results may also have implications for understanding visuo-spatial and object recognition deficits in VCFS, which also involve the inferior parietal lobule [5,17,22,30,51,58]. Supporting the hypothesis of inferior parietal lobe dysfunction, Simon et. al have shown that, compared with typically developing controls, children with VCFS have poor performance in neurocognitive tasks associated with inferior parietal regions: visual attentional orienting, visual enumeration, and relative numerical magnitude judgment [48].

Our results add to the increasing evidence that structural and functional impairments in inferior parietal lobe regions underlie developmental dyscalculia. In females with fragile X syndrome, there is reduced activation in the left supramarginal and bilateral angular gyri during arithmetic tasks compared with controls [42]. In adolescents who are born prematurely and have dyscalculia, gray matter is decreased in the left intraparietal sulcus compared with adolescents who were born prematurely but do not have dyscalculia [23]. Finally, in Turner syndrome, which also is associated with impaired arithmetic skills, grey matter density and depth of the right intraparietal sulcus are both reduced [34]. Subjects with Turner syndrome also show reduced activation in the right intraparietal sulcus compared with control subjects during exact calculation with large numbers [33].

Our results are preliminary and require replication with more extensive assessment of arithmetic abilities and larger samples. However, these findings highlight potential cognitive implications of white matter aberrations in VCFS. Understanding biological factors underlying cognitive deficits provides potential for improving effectiveness of future

assessment and intervention with children and adolescents affected by VCFS.

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