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ORIGINAL RESEARCH

Abnormal Left-Hemispheric Sulcal Patterns in Adults With Simple Congenital Heart Defects Repaired in Childhood

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BACKGROUND: Children operated on for a simple congenital heart defect (CHD) are at risk of neurodevelopmental abnormalities. Abnormal cortical development and folding have been observed in fetuses with CHD. We examined whether sulcal folding patterns in adults operated on for simple CHD in childhood differ from those of healthy controls, and whether such differences are associated with neuropsychological outcomes.

METHODS AND RESULTS: Patients (mean age, 24.5 years) who underwent childhood surgery for isolated atrial septal defect (ASD; n=33) or ventricular septal defect (VSD; n=30) and healthy controls (n=37) were enrolled. Sulcal pattern similarity to healthy controls was determined using magnetic resonance imaging and looking at features of sulcal folds, their intersulcal relationships, and sulcal graph topology. The sulcal pattern similarity values were tested for associations with comprehensive neuropsychological scores. Patients with both ASD and VSD had decreased sulcal pattern similarity in the left hemisphere compared with controls. The differences were found in the left temporal lobe in the ASD group and in the whole left hemisphere in the VSD group (P=0.033 and P=0.039, respectively). The extent of abnormal left hemispheric sulcal pattern similarity was associated with worse neuropsychological scores (intelligence, executive function, and visuospatial abilities) in the VSD group, and special educational support in the ASD group.

CONCLUSIONS: Adults who underwent surgery for simple CHD in childhood display altered left hemisphere sulcal folding patterns, commensurate with neuropsychological scores for patients with VSD and special educational support for ASD. This may indicate that simple CHD affects early brain development.

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Key Words: adult ■ brain ■ congenital heart defect ■ magnetic resonance imaging ■ sulcal pattern

The long-term impact of a congenital heart defect (CHD) extends beyond cardiac morbidity. The brain seems particularly vulnerable to CHD, and many patients reveal morphological brain changes and experience neuropsychological impairments.[1–5] Accordingly, some degree of neurodevelopmental impairment or disability is found in up to 50% of children with complex CHD[3,4,6] and 27% of adults with simple CHD.[5] Although neurodevelopmental impairments are increasingly recognized as the most common long-term sequela in CHD, the underlying mechanisms remain unclear.

Neurodevelopmental impairments in CHD may be observed already during infancy.[7] Neonatal brain

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study to characterize the cerebral sulcal folding patterns in surgically approached simple congenital heart defects compared with healthy controls.
- Abnormal left-hemispheric sulcal patterns were present in a cohort of surgical approached patients with simple congenital heart defects and associated with poorer neurodevelopmental outcomes.
- Differences in sulcal depth patterns were the main contributor to the abnormal sulcal patterns in the simple congenital heart defects.

What Are the Clinical Implications?

- The abnormal sulcal folding patterns may indicate that simple congenital heart defect affects early brain development, and may be a contributive factor to the neurodevelopmental challenges previously demonstrated in this population.
- These results emphasize the need for additional research on potential interventions in this population, and it seems particularly important to identify what may be modifiable and what may not be modifiable in this population.

Nonstandard Abbreviations and Acronyms

GM	gray matter
WM	white matter

injuries[8] and altered brain development[9] are present even before cardiac surgery, suggesting that the brain is vulnerable to CHD already in utero. This notion is supported by third-trimester findings of brain growth failure in CHD fetuses, resulting in lower total brain volumes and metabolism.[10] This growth failure seemingly affects gray matter (GM), reducing the surface area of fetal cortical GM and impairing the normal folding of the cortex into gyri and sulci.[11] Indeed, cortical and subcortical GM are noted to be particularly vulnerable structures in complex CHD during infancy.[12]

The human fetus' cerebral cortex folds as cortical neurons differentiate, develop, and attain specific functions. The primary cortical sulci develop early and are relatively preserved across individuals, separating cortical regions with specific functions and cytoarchitectural characteristics.[13] These sulci have developed by the third trimester, whereas more variable secondary and tertiary sulci form until gestation.[14] The actual folding is thought to be the combined effects of genetically programmed "protomaps" that orchestrate cortical development, and the accompanying physical forces as connected cell structures evolve and grow.[15] Possibly as a result of the link between brain development and cortical folding in the third trimester, premature birth and intrauterine growth restriction can be accompanied by parallel changes in abnormal folding patterns and functional deficits.[16,17] Altered hemodynamics in fetuses with CHD may cause lower brain tissue oxygenation and possibly affect brain development.[18,19] In support of a link between in utero cortical maturation and morphological brain changes in later life, altered sulcal patterns, as quantified from magnetic resonance imaging (MRI) data, have been demonstrated in both fetuses and adolescents with complex CHD.[20,21] Moreover, strong associations exist between abnormal sulcal patterns and neurodevelopmental impairments in complex CHD.[20]

The aim of this study was to better understand cortical folding abnormalities in subjects with simple CHD to clarify factors that may contribute to their cerebral vulnerability. We applied a novel quantitative sulcal pattern analysis technique[22] to evaluate for early differences in brain development between adults operated on for simple CHD in childhood and their normally developing peers. We hypothesized that individuals with simple CHD would have measurable alteration of their sulcal patterns.

METHODS

Design and Study Population

The study was approved by the Regional Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 1-10-72-233-17) and the Danish Data Protection Agency (chart: 2012-58-006), and complies with the World Medical Association's Declaration of Helsinki. In compliance with Danish law, all participants provided written informed consent before enrollment. The study is listed on clinicaltrials.gov (identifier: NCT03871881). The data that support the findings of this study are available from the corresponding author on reasonable request.

The study cohort is part of a prospective, cross-sectional study that investigates the neurodevelopmental outcome in simple CHD.[5] In this study, all the participants underwent a brain MRI and a battery of neuropsychological tests. Inclusion criteria were as follows: (1) diagnosis of isolated atrial septal defect (ASD) or (2) isolated ventricular septal defect (VSD) with surgical defect closure between 1990 and 2000. Exclusion criteria were as follow: (1) coexistence of other CHDs, (2) associated syndromes (eg, Down and DiGeorge syndrome), (3) contraindications for MRI, (4) recent head

trauma, and (5) lack of Danish language skills. Surgical treatment was performed at Aarhus University Hospital, and has previously been described.[5] A group of healthy volunteers, without history of cardiac disease and matched on age, sex, and educational attainment, was included as a control group. They were approached through local flyers and internet-based announcements.

MRI Acquisition and Processing

MRI was performed on a Siemens Magnetom Prisma 3-T MRI system with a 32-channel head coil. Subjects were scanned using a magnetization-prepared 2 rapid acquisition gradient echo (MP2RAGE) sequence with the following parameters: repetition time, 6.5 seconds; inversion time 1, 0.5 seconds; inversion time 2, 2.9 seconds; α1, 4°; α2, 7°; and 3-dimensional sequence imaged at isotropic 0.9-mm resolution (acquisition matrix, 240×256; 192 sagittal slices) with turbo factor of 144, as defined by others.[23] All images were inspected by a neuroradiologist to ensure data quality and detect structural abnormalities (eg, tumors and stroke). MP2RAGE images were preprocessed, normalized, and segmented, as previously described.[5] Cortical surfaces were extracted using fast accurate cortex extraction (FACE).[24,25] In FACE, topologically correct surface meshes are iteratively fitted to the white matter (WM)–GM boundary and the GM-pia boundary with subvoxel precision. FACE has been shown to be robust, accurate, and fast.[26] All the reconstructed surfaces were visually inspected for each subject to ensure accuracy.

Quantitative Sulcal Pattern Analysis

The reconstructed cortical models of the WM surface (GM/WM boundary) were automatically parcellated into anatomical regions based on lobar and gyral/sulcal structure. The 2-dimensional surface registration algorithm was used to align each subject to the unbiased surface group template generated from the International Consortium for Brain Mapping 152 data set.[27,28] The lobar and sulcal labels created on the template[29] were mapped onto a registered individual's surface. The left and right whole hemispheres and lobar regions were then used for sulcal pattern analysis in this study.

The sulcal pattern was represented using a graph structure with sulcal pits and their surrounding catchment basins as nodes that characterize the global pattern of primary sulcal folds. Sulcal depth maps were generated on the WM surfaces using depth potential function[30] and smoothed with a full-width half maximum value of 10 mm to reduce noisy depth variations.[31] On the basis of the smoothed depth maps, the sulcal pits and their catchment basins were automatically identified using a watershed segmentation algorithm[32,33] and used as the nodes in the sulcal graph representation. If sulcal basins met, sulcal pits in those basins were connected with an edge.

The sulcal pattern graphs between different subjects were automatically compared using a spectral-based matching algorithm[22,34] by which a similarity measure that ranged from 0 to 1 was computed for each hemisphere and the lobar regions. An example of optimal sulcal pattern matching and similarity measure in the temporal lobe is shown in Figure 1. A value closer to 1 equals a higher similarity. The sulcal pattern comparison was performed using the following: (1) geometric features of sulcal folds (3-dimensional position and depth and area of sulcal pits and basins), (2) their intersulcal relationship, and (3) graph topology (the number of edges and paths between

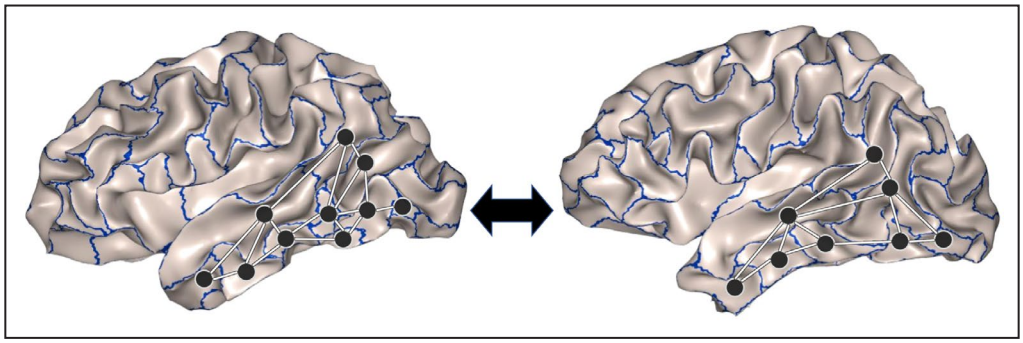

Figure 1. Example of the sulcal graph pattern matching and similarity measure (value from 0 to 1) in the temporal lobe between 2 subjects.
The black nodes in the graph structure represent sulcal pits and the corresponding sulcal basins (blue boundaries) that are automatically extracted on the white matter surface. When sulcal basins meet, sulcal pits in those basins are connected with an edge. The 2 sulcal graph patterns are optimally matched, and their similarity is measured by using the geometric features of the nodes (3-dimensional position and depth and area of sulcal basin), their relationship, and sulcal graph topology. A pair having high similarity shows more similar geometric features of nodes and their interrelationship and sulcal arrangement than the pair having low similarity.

neighborhood nodes).[22] A similarity measure was computed for all features combined (position, depth, area, and graph topology) and the similarity of each individual feature to evaluate its relative impact on the sulcal pattern similarity.

Using the graph-based sulcal pattern comparison method, sulcal pattern similarity for each of the study groups was automatically computed for the left and right hemispheres and lobes. The sulcal pattern similarity in the control group was the mean similarity value from the comparisons of each individual control subject with the other 36 control subjects. In the CHD group, the similarities were the mean similarity value obtained from the comparisons of each CHD subject with the 37 controls. Each CHD subject therefore had a mean similarity with all 37 controls. The mean similarity within the CHD groups could then be compared with the mean similarity in the control group. These methodological procedures are explained in more detail in previous studies.[22,32]

Sulcal Pattern Symmetry Analysis

A further evaluation of sulcal pattern symmetry was made by measuring similarity between the left and right hemispheric and lobar sulcal patterns. The left hemisphere cortical surface was flipped along the mid–sagittal plane and compared with the right hemisphere cortical surface. A lower similarity value between left and right indicates asymmetric sulcal pattern between hemispheres. The combined feature in sulcal pattern similarity was used to compare the left-right sulcal pattern symmetries in the participants with CHD with the control group.

Sulcal Depth Analysis

If a hemisphere or its brain regions showed lower sulcal pattern similarity values in the CHD group, an evaluation of sulcal depth maps was performed in that hemisphere. The sulcal depth maps of participants with CHD were compared with the maps of the control group. Sulcal depth maps on the WM surface were generated as described in the Methods sections above. Sulcal depth values were determined using a measure of convexity of the cortical surface as depth potential.[30] The sulcal depth measure ranged from negative to positive values, with lower values indicating a larger sulcal depth. We performed sulcus-wise analysis of sulcal depth based on the primary sulcal labels that were registered and mapped from the International Consortium for Brain Mapping 152 surface group template.[27–29] We averaged the sulcal depth for 19 primary sulcal regions and performed statistical group comparisons (Sylvian fissure and central, superior frontal, middle frontal, inferior frontal, precentral, postcentral, intraparietal, superior temporal, inferior temporal, occipitotemporal, collateral, orbital, olfactory, cingulate, subparietal, lateral occipital, calcarine, and parieto-occipital sulci).

Neurodevelopmental Assessment

The neurodevelopmental function was assessed using a neuropsychological test battery with assessment of intelligence, executive functions, visuospatial learning and memory, verbal learning, and memory and social cognition, as previously described.[5]

Statistical Analysis

Data are reported as mean±SD, absolute numbers with percentages of participants, or as medians with total range, as appropriate. Continuous data were compared using the Student unpaired *t*-test or Wilcoxon rank-sum test, as appropriate, for normally and nonnormally distributed data, respectively. Binary data were compared using the χ^2 test. Correlations were performed using simple linear regression in an unadjusted model. Statistical significance is considered as $P<0.05$.

The whole left and right hemispheric sulcal pattern similarities between groups were compared for the combined set of all features (sulcal position, depth, area, and graph topology) as well as for the individual features. The sulcal pattern similarities between groups in lobar regions were compared for the combined feature, and if statistically significant, the lobe-specific individual features of sulcal pattern similarities were compared to evaluate the impact of each feature on the similarity. The depth values of the Sylvian fissure and primary sulci in the left and right hemisphere were compared between groups. Brain regions with differences in sulcal pattern similarity between groups were examined for associations with neurodevelopmental outcome using Pearson correlation coefficient and simple linear regression. All statistical analyses were conducted on a blinded data set using Stata/SE 15.1 for Mac (StataCorp, College Station, TX).

Sample Size Justification

A power analysis was made on the basis of previously published data on sulcal pattern similarity (the area feature in the right frontal lobe; Table 1.[20]) in adolescents with complex CHD. With a sample size of 63 patients with CHD and 37 control subjects, and a significance level of 0.05 using the Student *t* test, our primary outcomes would have a power of 81%.

RESULTS

Cohort

A total of 66 subjects with CHD (34 with ASD and 32 with VSD) and 40 controls were enrolled during the

Table 1. Demographics and Educational Attainments for Participants With CHDs and Control Participants

Variable	Participants With CHDs (n=63)	Control Participants (n=37)	*P* Value
At inclusion			
Age at testing, y	24.5±5.0	25.6±4.6	0.898
Height, cm	171±11	175±8	0.069
BMI, kg/m^2	24.5±4.1	23.0±3.3	0.054
Men, n (%)	20 (32)	13 (35)	0.728
Educational attainment			
ISCED primary education, n (%)	3 (5)	0 (0)	0.178
ISCED secondary education, n (%)	46 (73)	23 (62)	0.257
ISCED tertiary education, n (%)	14 (22)	14 (38)	0.093
Educational psychologist counseling, n (%)*	10 (16)	0 (0)	0.011†
Special education, n (%)‡	29 (46)	6 (16)	0.003†
Dyslexia, n (%)	11 (17)	0 (0)	0.007†
Dyscalculia, n (%)	4 (6)	0 (0)	0.115

Data are presented as mean±SD or as absolute numbers with relative percentages. BMI indicates body mass index; CHD, congenital heart defect; and ISCED, International Standard Classification of Education 2011.

*Received educational psychologist counseling during primary or secondary school.

†$P<0.05$.

‡Received special educational needs support during primary or secondary school.

study period from March 2018 to November 2018. Three patients felt claustrophobic/anxious during MRI and could not complete the study. Moreover, MRI scans of 3 control subjects were excluded because of inadequate image quality. In total, MRI data from 63 participants with CHD (33 with ASD and 30 with VSD) and 37 controls were included in the analyses. The demographics and educational attainment are shown in Table 1, and perioperative information is shown in Table 2. The study participants' medical history was previously described.[5]

Sulcal Pattern

The participants with ASD and VSD disclosed a decreased sulcal pattern similarity in the left but not in the right hemisphere compared with control subjects, as shown in Table 3. Group differences were demonstrated in different left hemispheric regions; the ASD group had a lower combined sulcal pattern similarity in the left temporal lobe and the VSD in the whole left hemisphere compared with controls (P=0.033 and P=0.039, respectively). In cortical regions with significant differences in the combined feature, a further analysis of the individual features revealed a lower similarity in sulcal depth patterns in the whole left hemisphere in both the ASD and VSD groups (P=0.049 and P=0.023, respectively) and in the temporal lobe in ASD group compared with controls (P=0.017).

Sulcal Pattern Left-Right Symmetry

Similarity between the sulcal pattern on the left and right hemispheres in the CHD groups was not different from that in controls, as shown in Table 4. Further analysis of similarity between the left and right hemisphere in individual features was therefore not computed.

Sulcal Depth

As the main differences in sulcal pattern similarity features were attributed to sulcal depth patterns in the left hemisphere, we examined the depths of sulci across that entire cortical region. The participants with ASD and VSD demonstrated several left hemispheric sulci with differences in depth compared with the controls, as shown in Table 5. Main findings were increased depth of sulci in the left frontal lobe (middle frontal sulcus) in both the ASD and VSD groups, and furthermore, increased depths of sulci in the left frontoparietal (cingulate sulcus) and occipital (lateral occipital sulcus) lobes in the VSD group and decreased depth of sulci in the left temporal lobe (inferior temporal sulcus) in the ASD group. In addition, we also examined the sulcal depths across the right hemisphere that, similar to the findings in the left cerebral hemisphere, showed increased depth of sulci in the right frontal and frontoparietal lobe in the ASD and VSD groups (Table S1).

Neurodevelopmental Outcomes and Sulcal Analysis

Neuropsychological test outcomes previously reported in the participants with CHD[5] were correlated with sulcal pattern similarity values. Only regions with significantly lower combined feature values in the

Table 2. Perioperative Information for the Participants With ASDs and VSDs

Variable	Participants With ASDs (n=33)	Participants With VSDs (n=30)
Age at diagnosis, y	5.8±6.6	0.5±1.0
Age at surgery, y	7.0±6.2	1.7±1.4
Defect size, mm	16.6±9.1	8.3±4.0
Total bypass time, min	43±20	59±21
Cross-clamp time, min	16±9	30±14
Hospital stay >14 d, n (%)	0 (0)	3 (10)
ICU stay >1 d, n (%)	4 (12)	10 (33)
Preoperative catherization, n (%)	4 (12)	12 (40)
Mean pulmonary-to-systemic blood flow ratio (Qp/Qs)	2.4±0.9	2.8±1.1
ASD defect type, n (%)		
Primum	2 (6)	…
Secundum	31 (94)	…
ASD defect closure, n (%)		
Direct suture	17 (52)	…
Dacron patch	13 (39)	…
Pericardial patch	3 (9)	…
VSD defect type, n (%)		
Perimembranous	…	16 (53)
Muscular	…	14 (47)
VSD defect closure, n (%)		
Patch	…	19 (63)
Direct suture	…	11 (37)
Pulmonary artery banding, n (%)	…	3 (10)
Persisting ductus arteriosus closure	…	2 (7)

Data are presented as mean±SD or as absolute numbers with relative percentages. ASD indicates atrial septal defect; ICU, intensive care unit; and VSD, ventricular septal defect.

participants with CHD were tested. Significant associations were observed between the sulcal pattern similarity for the whole left hemisphere in the VSD group and several neuropsychological test outcomes of intelligence, executive function, and visuospatial learning and memory, as shown in Figure 2A through 2E and Table 6. Adjustment for dyslexia did not change the statistical significance of the associations. These associations were unique for the VSD group as the specific associations were not present in the control group. No significant associations were found in the ASD group (Table S2). An additional subgroup analysis of the 46% of the participants with CHD (VSD=13 and ASD=16) who had received special education (Table 1) revealed significantly lower neuropsychological test outcomes on intelligence (full-scale intelligence quotient; P=0.008), executive function (executive composite score; P=0.012), and social recognition (P=0.029) measures, compared with participants with CHD who did not receive special education. Moreover, a lower sulcal pattern similarity was observed in the ASD group (left temporal depth feature; P=0.049), but not in the VSD group, who had received special education compared with patients who had not received special education.

DISCUSSION

Herein, we describe the first sulcal pattern analysis of adult subjects who underwent surgery for isolated ASD or VSD during childhood, and demonstrate important associations between sulcal pattern and neurodevelopmental outcomes. In subjects with simple CHD, the left cerebral hemisphere sulcal patterns had reduced similarity compared with control subjects. Abnormal sulcal patterns were demonstrated in the whole left hemisphere in the VSD group, and in the left temporal lobe in the ASD group. When evaluating individual sulcal features, the sulcal depth feature showed a difference in sulcal patterns in both the ASD and VSD groups, indicating the importance of this specific feature in the related sulcal pattern differences observed in this patient cohort. These novel findings concur with previous reports of abnormal brain development in CHD, and extend existing knowledge by revealing that subtle cortical changes exist in adults with simple CHD with relevant neurodevelopmental associations.

Atypical Sulcal Patterns

In accordance with our findings, similar leftward biased differences in sulcal pattern have been demonstrated in fetuses and adolescents with CHD.[20,21] Ortinau et al reported altered global sulcal patterns in the left hemisphere in fetuses with moderate to severe CHD compared with typically developing fetuses.[21] Morton et al demonstrated abnormal sulcal patterns in the left hemisphere, including the temporal lobe, and associations with neurodevelopmental outcomes in adolescents with single-ventricle physiological CHD.[20] The abnormal sulcal patterns in the ASD and VSD groups in our study were mainly attributed by alterations in sulcal depths, whereas in fetuses and adolescents with moderate to severe CHD, the altered sulcal patterning was mainly explained by differences in the sulcal area and sulcal position.[20,21] This may be descriptive of the differences in sulcal patterns between the simple and complex types of CHD, and therefore, the extent and characteristics of sulcal pattern abnormalities may reflect CHD severity. In summary, our findings indicate an abnormal cortical development in patients with simple CHD, and emphasize the current presumption of an abnormal long-term cerebral outcome in patients with CHD.

Table 3. Sulcal Pattern Similarity Values for the Participants With ASDs, Participants With VSDs, and Control Participants

Location	Sulcal Pattern Feature	ASD (n=33)	VSD (n=30)	Control (n=37)	*P* Value, ASD vs Control	*P* Value, VSD vs Control
Left hemisphere	Combined	0.7855±0.0040	0.7839±0.0063	0.7865±0.0038	0.265	0.039*
	Position	0.7707±0.0040	0.7692±0.0085	0.7714±0.0045	0.499	0.192
	Depth	0.8346±0.0047	0.8340±0.0056	0.8368±0.0044	0.049*	0.023*
	Area	0.9542±0.0016	0.9539±0.0019	0.9539±0.0019	0.504	0.929
	Graph topology	0.8539±0.0073	0.8522±0.0071	0.8535±0.0076	0.832	0.449
Left frontal	Combined	0.7910±0.0053	0.7900±0.0061	0.7907±0.0056	0.817	0.585
Left temporal	Combined	0.7760±0.0117	0.7771±0.0134	0.7811±0.0077	0.033*	0.135
	Position	0.7648±0.0145	0.7648±0.0124	0.7682±0.0109	0.269	0.235
	Depth	0.8161±0.0114	0.8204±0.0125	0.8226±0.0106	0.017*	0.446
	Area	0.9471±0.0039	0.9470±0.0064	0.9483±0.0037	0.203	0.305
	Graph topology	0.8655±0.0203	0.8639±0.0235	0.8685±0.0138	0.459	0.321
Left parietal	Combined	0.7757±0.0087	0.7739±0.0098	0.7760±0.0064	0.857	0.288
Left occipital	Combined	0.7836±0.0112	0.7782±0.0133	0.7836±0.0108	0.997	0.069
Right hemisphere	Combined	0.7833±0.0047	0.7832±0.0068	0.7833±0.0043	0.984	0.954
Right frontal	Combined	0.7893±0.0064	0.7914±0.0071	0.7896±0.0057	0.865	0.254
Right temporal	Combined	0.7777±0.0120	0.7750±0.0130	0.7772±0.0113	0.860	0.466
Right parietal	Combined	0.7700±0.0081	0.7684±0.0131	0.7710±0.0085	0.595	0.316
Right occipital	Combined	0.7781±0.0099	0.7818±0.0114	0.7800±0.0090	0.417	0.468

Data are presented as mean±SD. ASD indicates atrial septal defect; and VSD, ventricular septal defect.
*$P<0.05$.

Similar Asymmetry of Sulcal Patterns

The hemispheres of the brain are structurally asymmetric,[35] and asymmetry of the cortical structures occurs during normal childhood development, likely reflecting continuous brain maturation.[36] An increased hemispheric asymmetry, as shown in single-ventricle CHDs (attributable to increased sulcal pattern disruption in the left hemisphere),[20] may suggest an adverse amplification of the typical asymmetric cortical development. Fetuses[21] and infants[37] with CHD are also shown to have more left-sided than right-sided abnormalities in global sulcal pattern and cortical folding, respectively. We found a similar level of hemispheric asymmetry in adult subjects with ASD and VSD compared with control subjects, and therefore, the normal asymmetric development of cortical structures appears unaffected by simple CHD.

Atypical Sulcal Depths

The demonstrated abnormalities in sulci depth are in accordance with previously reported alterations in cortical sulcation present before surgery, in infants with complex CHD.[37] Hence, our findings may partly be related to alterations in early brain development. The atypical sulcal depth cannot entirely explain the altered sulcal depth pattern similarity; nevertheless, it underscores the importance of the sulcal depth pattern measure as a major contributor to the altered sulcal patterning in simple CHD.

Neurodevelopmental Outcomes and Sulcal Analysis

We have previously reported impaired neurodevelopmental outcomes in simple CHD compared with matched controls and population means.[5] Interestingly, significant associations were found between the previously reported neuropsychological test outcomes (full-scale intelligence quotient, perceptual reasoning, processing speed, executive function, and visuospatial learning and memory) and abnormal whole left hemispheric sulcal patterns in the VSD group. In accordance with our findings, Morton et al reported significant associations between executive function and left temporal lobe sulcal pattern similarity, and between processing speed and left frontal lobe sulcal pattern similarity, in a cohort of adolescents with single-ventricle physiological CHD.[20] Hence, the associations between altered sulcal patterning and impaired neurocognitive test scores may indicate an impact of CHD physiological features on brain development that confines neurocognitive abilities.

The additional subgroup analysis on patients with simple CHDs who received special education revealed

Table 4. Sulcal Pattern Left-Right Symmetry for the Participants With ASDs, Participants With VSDs, and Control Participants

Location	ASD (n=33)	VSD (n=30)	Control (n=37)	*P* Value, ASD vs Control	*P* Value, VSD vs Control
Hemispheres	0.7990±0.006	0.7997±0.009	0.7964±0.012	0.510	0.213
Frontal lobes	0.8047±0.013	0.8029±0.014	0.7998±0.015	0.149	0.387
Temporal lobes	0.7956±0.024	0.7890±0.023	0.7963±0.020	0.894	0.168
Parietal lobes	0. 7862±0.020	0.7872±0.025	0.7893±0.021	0.531	0.708
Occipital lobes	0.8021±0.027	0.7996±0.023	0.8029±0.028	0.904	0.607

Data are presented as mean±SD. ASD indicates atrial septal defect; and VSD, ventricular septal defect.

this subgroup as reflective of a more impacted population. We speculate whether the lower sulcal pattern similarity demonstrated in the ASD group, but not in the VSD group, who received special education, may be explained by a general heterogenicity among patients with ASD, whereas the patients with VSD may compose a more homogeneous group.

Potential Mechanisms

The fetal brain has high metabolic demands toward end gestation. Within the fetal brain, tissue oxygen levels play a key role in the proliferation and differentiation of nerve cells and the formation of the microvasculature needed to support their metabolic demands.[38,39] To secure a sufficient tissue oxygen level, the brain is protected against hypoxia by a range of protective mechanisms at this early stage in development.[40] In fetuses with complex CHD, however, blood oxygenation measurements suggest that brain tissue oxygen tension is lower than in the normal fetus, possibly explaining their altered brain development.[18,19]

The ASD and VSD are left to right shunt, acyanotic conditions, and thus expected to have a normal oxygen delivery to the brain during fetal development. Nevertheless, these conditions, and especially the VSDs, are associated with significant congestive heart failure and a particularly failure to thrive during childhood. For patients with simple CHD, who fall off the growth curve during the first year of life, a pivotal period

Table 5. Left Hemisphere Sulcal Depth Values for the Participants With ASDs, Participants With VSDs, and Control Participants

Left Hemisphere Sulcal Regions	ASD (n=33)	VSD (n=30)	Control (n=37)	*P* Value, ASD vs Control	*P* Value, VSD vs Control
Sylvian fissure	−0.6120±0.0551	−0.6313±0.1194	−0.6119±0.0729	0.995	0.416
Central sulcus	0.1195±0.0648	0.1326±0.1034	0.1468±0.0768	0.116	0.522
Superior frontal sulcus	−0.9752±0.3186	−0.8922±0.3720	−0.8709±0.3036	0.165	0.797
Middle frontal sulcus	0.1245±0.1287	0.1082±0.1217	0.1847±0.1104	0.039*	0.009*
Inferior frontal sulcus	0.3044±0.2300	0.2765±0.1701	0.2996±0.1719	0.920	0.586
Precentral sulcus	−0.1232±0.1018	−0.1456±0.1213	−0.1364±0.0991	0.582	0.733
Postcentral sulcus	0.0855±0.1652	0.0778±0.1456	0.0598±0.1388	0.482	0.607
Intraparietal sulcus	−0.6204±0.1655	−0.6849±0.1943	−0.6032±0.1611	0.662	0.064
Superior temporal sulcus	−0.2693±0.1238	−0.3147±0.1368	−0.2801±0.0834	0.668	0.207
Inferior temporal sulcus	0.4775±0.2201	0.4059±0.2463	0.3734±0.1733	0.031*	0.529
Occipitotemporal sulcus	−0.0194±0.1501	0.0523±0.2293	0.0573±0.1811	0.059	0.921
Collateral sulcus	0.1878±0.1388	0.1650±0.1508	0.1404±0.1449	0.168	0.500
Orbital sulcus	0.1785±0.1267	0.1517±0.1189	0.2121±0.1151	0.249	0.039*
Olfactory sulcus	0.5914±0.1835	0.5604±0.1682	0.5476±0.1309	0.251	0.728
Cingulate sulcus	−0.9811±0.0875	−1.0190±0.1193	−0.9526±0.0815	0.163	0.009*
Subparietal sulcus	0.4592±0.1388	0.4531±0.1375	0.4352±0.1236	0.446	0.576
Lateral occipital sulcus	0.4777±0.2305	0.4264±0.1842	0.5379±0.1901	0.236	0.018*
Calcarine sulcus	−0.5482±0.1666	−0.5565±0.1563	−0.5443±0.1432	0.918	0.740
Parieto-occipital sulcus	−0.4128±0.1707	−0.3751±0.1894	−0.4396±0.1580	0.497	0.134

Data are presented as mean±SD. The sulcal depth measures range from negative to positive values, with lower values indicating a larger sulcal depth. ASD indicates atrial septal defect; and VSD, ventricular septal defect.

*$P<0.05$.

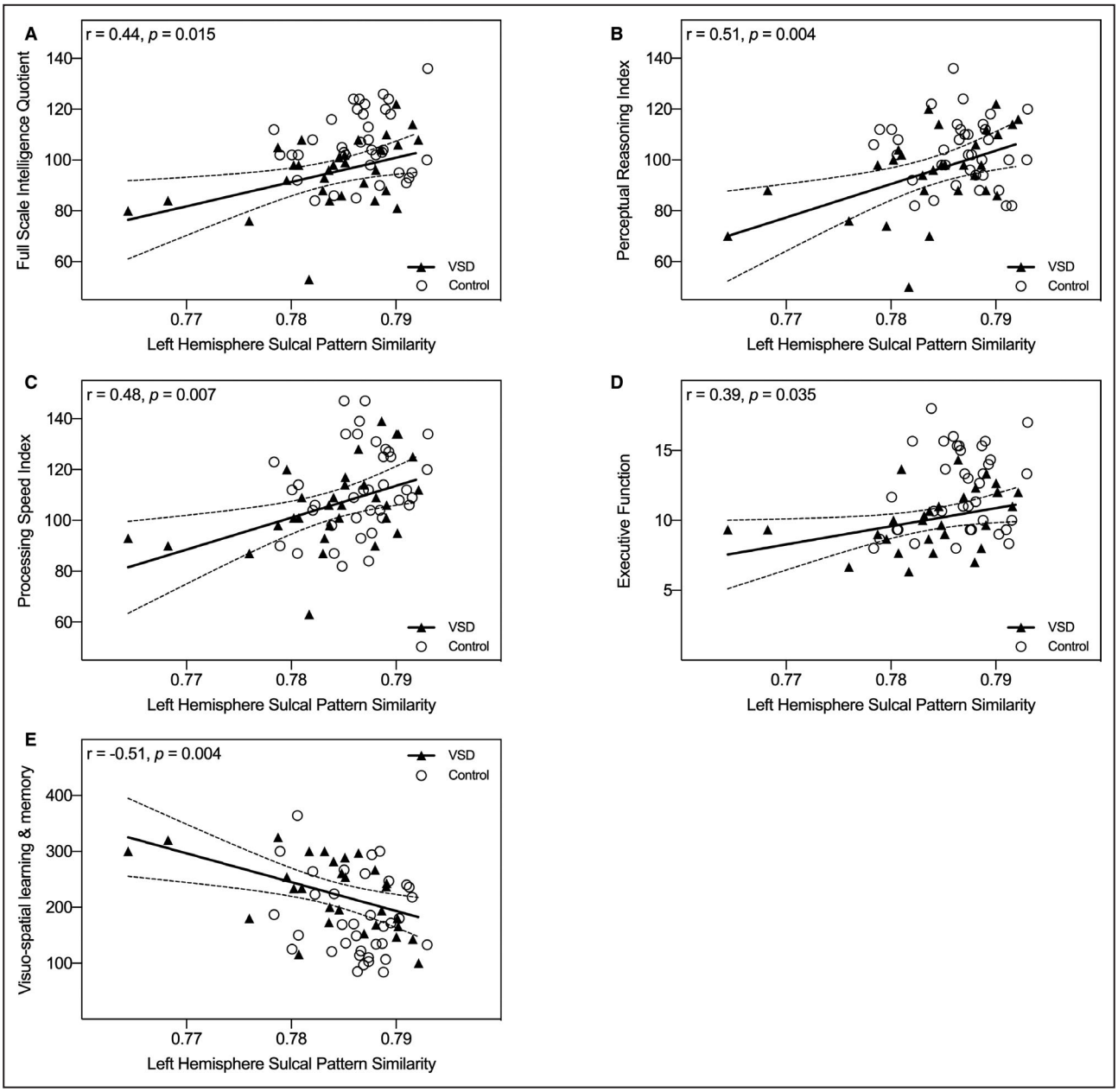

Figure 2. Unadjusted association between neurodevelopmental outcomes and sulcal pattern similarity for the participants with a ventricular septal defect (VSD).
Pearson correlation coefficients (*r*) and corresponding *P* values are shown. **A**, The left hemisphere sulcal pattern similarity and full-scale intelligence quotient (IQ). **B**, Left hemisphere sulcal pattern similarity and Perceptual Reasoning Index (PRI). **C**, Left hemisphere sulcal pattern similarity and Processing Speed Index (PSI). **D**, Left hemisphere sulcal pattern similarity and executive function. **E**, Left hemisphere sulcal pattern similarity and visuospatial learning and memory. The full-scale IQ, PRI, and PSI were measured using the Wechsler Adult Intelligence Scale–Fourth Edition and use scaled scores corresponding to the population mean of 100 (SD, ±15). Executive function represents the Design Fluency Test, a subtest of the Delis-Kaplan Executive Function System using scaled scores with an expected mean of 10 (SD, ±3). The visuospatial learning and memory represents the Time to Copy Trail of the Rey-Osterrieth Complex Figure Test using time measured in seconds. In the full-scale IQ, PRI, PSI, and Design Fluency Test, a higher score indicates a better performance; and in the Time to Copy Trail, a higher score indicates a poorer performance.

for brain growth and maturation, it is conceivable that brain development can be impacted in the same way as the whole-body development can be affected. Hence, it is conceivable that impaired postnatal brain growth secondary to heart failure might account for the more severe brain abnormalities and developmental findings in the patients with simple CHD.

With the previously identified hereditary in ASD and VSD[41] and a shared genetic contribution to CHD and neurodevelopmental disabilities,[42] a possible genetic link

Table 6. Association Between Neuropsychological Outcomes and Left Hemisphere Sulcal Pattern Similarity for the Participants With VSDs

Association	VSD (n=30)			
	R^2	β±SE	*t* Value	*P* Value
Intelligence*				
Full-scale IQ	0.195	0.000204±0.000078	2.60	0.015†
Verbal comprehension	0.015	0.000055±0.000084	0.66	0.513
Perceptual reasoning	0.256	0.000195±0.000064	3.10	0.004†
Working memory	0.047	0.000097±0.000082	1.18	0.248
Processing speed	0.231	0.000184±0.000064	2.90	0.007†
Executive function‡				
Executive composite score	0.090	0.000929±0.000558	1.67	0.107
Trail making	0.062	0.000579±0.000426	1.36	0.185
Verbal fluency	0.014	0.000249±0.000389	0.64	0.528
Design fluency	0.149	0.001149±0.000519	2.21	0.035†
Color-word interference	0.064	0.000685±0.000495	1.38	0.177
Visuospatial learning and memory§				
Copy	0.009	0.001297±0.002535	0.51	0.613
Time to copy	0.264	−0.000051±0.000017	−3.11	0.004†
Immediate recall	0.003	0.000023±0.000087	0.27	0.790
Delayed recall	0.001	0.000015±0.000118	0.13	0.900
Recognition	0.056	−0.003031±0.002353	0.21	0.208
Auditory learning and memory‖				
Trial 1	0.023	−0.000090±0.000111	−0.81	0.422
Total learning	0.024	0.000087±0.000105	0.83	0.415
Delayed recall	0.000	0.000006±0.000119	0.05	0.961
Recognition	0.013	−0.002081±0.003410	−0.61	0.547
Social cognition				
Reading the mind in the eyes test	0.001	0.000025±0.000124	0.20	0.844

Data are presented as R^2, β±SE, *t* value, and *P* value. IQ indicates intelligence quotient; and VSD, ventricular septal defect.
*Wechsler Adult Intelligence Scale–Fourth Edition.
†$P<0.05$.
‡Delis-Kaplan Executive Function System.
§Rey-Osterrieth Complex Figure Test.
‖Rey Auditory Verbal Learning Test.

between the heart and brain development may occur; hence, genetic contributions may also be relevant to the cause of altered sulcal patterning in simple CHD.

Implications and Future Research

Our findings should be considered as an effort to characterize the cortical development and to expand the existing knowledge on neurodevelopment in simple CHD. The relevance of these results should be seen in the light of our previous findings of increased morbidity[43,44] and mortality,[45,46] a poorer affiliation to the work force, as well as lower education rate and high prevalence of psychiatric morbidity[47,48] in those with isolated septal defects compared with the general population.

Our results emphasize a need for additional research on potential interventions in this population, and it seems particularly important to identify what may be modifiable and what may not be modifiable in this population.

Limitations

The current study has notable limitations. First, the findings are based on a single time point for a subset of patients in a limited sample size. A follow-up study, testing over several points of development, would increase the ability to detect changes in cortical development, and a larger study cohort would allow a meaningful comparison of subgroups (eg, ASD and VSD subtypes). Nevertheless, our sample of adults with simple CHD has previously shown enough power to allow a meaningful comparison of neurodevelopmental metrics.[5] Second, our cohort of adults with simple CHDs was substantially older at surgery than

would be the case for a similar cohort of current-day patients. Our results may therefore not reflect sulcal pattern abnormalities in today's operated on patients with ASD and VSD. However, as the cause of altered sulcal patterning is unclarified and may be related to the prenatal and postnatal period of brain development, sulcal pattern abnormalities may continue to be a problem in today's patients. Third, genetic contributions to our findings cannot be excluded because of lack of genetic testing. Last, as changes in cortical folding have previously been shown in newborns with intrauterine growth restriction,[17] birth-related information (eg, gestational age and birth weight) is important, as it may be a source of confounding. However, it was not possible to obtain birth-related metrics for the included study cohort.

CONCLUSIONS

We identified abnormal sulcal patterns among adults, who in childhood underwent surgical closure of a simple CHD, when compared with healthy peers. The sulcal pattern differences were present in the left but not the right hemisphere in both ASDs and VSDs, and were partly explained by differences in sulcal depth patterns. These differences in sulcal pattern similarity were associated with poorer neurodevelopmental outcomes in the VSD group. Our findings imply the presence of abnormal left-hemispheric sulcal patterns in surgical approached patients with ASD and VSD and may be considered as reflective of an atypical early neurodevelopment.

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Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Right hemisphere sulcal depth values for the atrial septal defect (ASD), ventricular septal defect (VSD) and control participants.

Left Hemisphere sulcal regions	ASD (n=33)	VSD (n=30)	Control (n=37)	*P* Value, ASD Versus Control	*P* Value, VSD Versus Control
Sylvian Fissure	-0.5886 ± 0.0670	-0.6438 ± 0.1098	-0.5870 ± 0.0724	0.926	0.014*
Central sulcus	0.1765 ± 0.0840	0.1763 ± 0.0956	0.1551 ± 0.1116	0.373	0.412
Superior frontal sulcus	-0.9142 ± 0.3179	0.0956 ± 0.3397	-0.6770 ± 0.3180	0.003*	0.066
Middle frontal sulcus	0.1786 ± 0.1458	0.1582 ± 0.1318	0.1466 ± 0.1301	0.335	0.719
Inferior frontal sulcus	0.3404 ± 0.1971	0.2591 ± 0.1790	0.3722 ± 0.1995	0.506	0.019*
Precentral sulcus	-0.1403 ± 0.0955	-0.1584 ± 0.1555	-0.1440 ± 0.1744	0.916	0.725
Postcentral sulcus	-0.0029 ± 0.1746	0.0534 ± 0.1870	0.0732 ± 0.1563	0.058	0.638
Intraparietal sulcus	-0.4864 ± 0.1779	-0.4799 ± 0.1678	-0.4350 ± 0.1504	0.195	0.253
Superior temporal sulcus	-0.2507 ± 0.1058	-0.2602 ± 0.1203	-0.2484 ± 0.0781	0.916	0.629

Inferior temporal sulcus	0.3492 ± 0.1566	0.3976 ± 0.1716	0.3303 ± 0.1187	0.570	0.063
Occipito-temporal sulcus	0.1050 ± 0.1958	0.0796 ± 0.2532	0.0487 ± 0.1488	0.178	0.536
Collateral sulcus	0.1349 ± 0.1520	0.0949 ± 0.1350	0.0920 ± 0.1220	0.194	0.925
Orbital sulcus	0.0068 ± 0.1139	0.0159 ± 0.1339	0.0959 ± 0.1022	0.001*	0.007*
Olfactory sulcus	0.7512 ± 0.1985	0.6970 ± 0.1637	0.6978 ± 0.2193	0.291	0.987
Cingulate sulcus	-0.8529 ± 0.0672	-0.8823 ± 0.1016	-0.8332 ± 0.0827	0.284	0.033*
Subparietal sulcus	0.5578 ± 0.1255	0.5390 ± 0.1691	0.4982 ± 0.1430	0.070	0.289
Lateral occiptial sulcus	0.4808 ± 0.1841	0.4481 ± 0.1370	0.4819 ± 0.1772	0.979	0.394
Calcarine sulcus	-0.6494 ± 0.2065	-0.6831 ± 0.1598	-0.5930 ± 0.1730	0.216	0.032*
Parieto-occipital sulcus	-0.5464 ± 0.1597	-0.5773 ± 0.1706	-0.5703 ± 0.1159	0.473	0.842

Data are presented as mean ± SD. The sulcal depth measures range from negative to positive values with lower values indicating a larger sulcal depth. * $p < 0.05$.

Table S2. Association between neuropsychological outcomes and left temporal sulcal pattern similarity in the atrial septal defect group.

	ASD (n = 33)				
Association	R^2	B	SE B	t	*P*
Intelligence †					
Full-scale IQ	0.002	0.000040	0.000157	0.25	0.803
Verbal comprehension	0.008	-0.000075	0.00015	-0.49	0.631
Perceptual Reasoning	0.001	0.000018	0.000140	0.13	0.901
Working memory	0.082	0.000278	0.000167	1.67	0.106
Processing Speed	0.004	-0.000046	0.000127	-0.36	0.720
Executive function ‡					
Executive Composite Score	0.016	0.000883	0.001251	0.71	0.486
Trail Making	0.002	0.000222	0.000983	0.23	0.822
Verbal Fluency	0.015	-0.000594	0.000879	-0.68	0.504
Design Fluency	0.002	-0.000220	0.000901	-0.24	0.809
Color-Word Interference	0.020	0.000703	0.000907	0.78	0.440
Visuo-spatial learning and memory §					
Copy	0.063	-0.008864	0.006146	-1.44	0.159
Time to Copy	0.021	0.000027	0.000034	0.81	0.426

Immediate Recall	0.000	-0.000012	0.000173	-0.07	0.946
Delayed Recall	0.003	-0.000065	0.000213	-0.31	0.761
Recognition	0.012	0.003875	0.006311	0.61	0.544
Auditory learning and memory ‖					
Trial 1	0.000	0.000017	0.000210	0.08	0.939
Total Learning	0.000	-0.000007	0.000200	-0.03	0.974
Delayed Recall	0.001	0.000044	0.000222	0.20	0.845
Recognition	0.092	0.012183	0.006868	1.77	0.086
Social Cognition					
Reading the Mind in the Eyes Test	0.008	-0.000114	0.00022	-0.51	0.614

Data are presented as unadjusted R^2, B ± standard error, t and p-value and from a linear regression model. R^2, R-squared; B, beta; SE, standard error; t; t-value; *P*, *p*-value. † Wechsler Adult Intelligence Scale version IV; ‡ Delis-Kaplan Executive Function System; § Rey-Osterreith Complex Figure Test; ‖ Rey Auditory Verbal Learning Test.