ORIGINAL RESEARCH

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

Benjamin Asschenfeldt (D), MD, PhD; Lars Evald (D), MSc, PhD; Hyuk Jin Yun (D), PhD; Johan Heiberg (D), MD, PhD, DMSc; Leif Østergaard (D), MD, PhD; P. Ellen Grant, MD, MSc; Vibeke Elisabeth Hjortdal (D), MD, PhD, DMSc; Kiho Im, PhD*; Simon Fristed Eskildsen (D), MSc, PhD*

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.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03871881.

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 CHD3,4,6 and 27% of adults with simple CHD.5 Although neurodevelopmental impairments are increasingly recognized as the most common long-term sequelae in CHD, the underlying mechanisms remain unclear.

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

| Abbreviation | Description |
|--------------|-------------|
| GM           | gray matter |
| WM           | white matter |

Injuries and altered brain development 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. 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. Indeed, cortical and subcortical GM are noted to be particularly vulnerable structures in complex CHD during infancy.

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. These sulci have developed by the third trimester, whereas more variable secondary and tertiary sulci form until gestation. 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. Possibly as a result of the link between brain development and cortical folding in the third trimester, premature birth and intratwining growth restriction can be accompanied by parallel changes in abnormal folding patterns and functional deficits. Altered hemodynamics in fetuses with CHD may cause lower brain tissue oxygenation and possibly affect brain development. 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. Moreover, strong associations exist between abnormal sulcal patterns and neurodevelopmental impairments in complex CHD.

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 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. 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 follows: (1) coexistence of other CHDs, (2) associated syndromes (eg, Down and DiGeorge syndrome), (3) contraindications for MRI, (4) recent head
Asschenfeldt et al Abnormal Sulcal Patterns in Simple CHD

trauma, and (5) lack of Danish language skills. Surgical treatment was performed at Aarhus University Hospital, and has previously been described. 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. 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.

Cortical surfaces were extracted using fast accurate cortex extraction (FACE). 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. 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. The lobar and sulcal labels created on the template 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 and smoothed with a full-width half maximum value of 10 mm to reduce noisy depth variations. On the basis of the smoothed depth maps, the sulcal pits and their catchment basins were automatically identified using a watershed segmentation algorithm 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 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 basin), (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.
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.27-28 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 χ² 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) 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
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 CHD5 were correlated with sulcal pattern similarity values. Only regions with significantly lower combined feature values in the
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 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.
The hemispheres of the brain are structurally asymmetric, and asymmetry of the cortical structures occurs during normal childhood development, likely reflecting continuous brain maturation. An increased hemispheric asymmetry, as shown in single-ventricle CHDs attributable to increased sulcal pattern disruption in the left hemisphere, may suggest an adverse amplification of the typical asymmetric cortical development. Fetuses and infants 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.

The demonstrated abnormalities in sulci depth are in accordance with previously reported alterations in cortical sulcation present before surgery, in infants with complex CHD. 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. 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 physiologic CHD. 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 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                   | 0.486                  |
| 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.
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. 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. 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.

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

| 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.

| Location | 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 | 0.1032±0.1271 | 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 | −0.8204±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.
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 and a shared genetic contribution to CHD and neurodevelopmental disabilities, a possible genetic link
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 and mortality, a poorer affiliation to the work force, as well as lower education rate and high prevalence of psychiatric morbidity 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. 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, 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.

ARTICLE INFORMATION

Received August 5, 2020; accepted January 4, 2021.

Affiliations

From the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus N, Denmark (B.A., J.H.); Department of Clinical Medicine, Aarhus University, Aarhus N, Denmark (B.A., L.E., J.H., L.O., V.E.H., S.F.E.); Hammel Neurorehabilitation Centre and University Research Clinic, Hammel, Denmark (L.E.); Center of Functionally Integrative Neuroscience, Aarhus University, Aarhus C, Denmark (L.O., S.F.E.); Fetal Neonatal Neuroimaging and Developmental Science Center (H.J.Y., P.E.G., K.J.) Division of Newborn Medicine (H.J.Y., P.E.G., K.J.) and Department of Radiology (P.E.G.), Boston Children’s Hospital, Boston, MA; (H.J.Y., P.E.G., K.J.) Department of Cardiothoracic Surgery, Rigshospitalet (V.E.H.) and Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (V.E.H.).

Sources of Funding

This study was supported by Aarhus University, Dagmar Marshalls Foundation, Aase & Einar Danielsens Foundation, The Danish Medical Association, A.P. Möller Foundation, Augustinus Foundation, the Health Research Fund of Central Denmark Region, and National Institute of Neurological Disorders and Stroke of the National Institutes of Health (RO1NS114067). Dr Hjortdal was financed on a grant from Novo Nordic Foundation project No. NNF3A170030576.

Disclosures

None.

REFERENCES

1. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. J Pediatr. 2007;151:73–78.e1.
2. Majnemer A, Limperopoulos C, Shevell M, Rosenblatt B, Rohlicek C, Tchervenkov C. Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. J Pediatr. 2006;148:72–77.
3. Bellinger DC, Wypij D, Rivkin MJ, Demaso DR, Robertson RL, Dunbar-Masterson C, Rappaport LA, Wernovsky G, Jonas RA, Newburger JW. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. Circulation. 2011;124:1361–1369.
4. Bellinger DC, Watson CG, Rivkin MJ, Robertson RL, Roberts AE, Stopp C, Dunbar-Masterson C, Bernson D, DeMaso DR, Wypij D, et al. Neuropsychological status and structural brain imaging in adolescents with single ventricle who underwent the Fontan procedure. J Am Heart Assoc. 2015;4:e002302. DOI: 10.1161/JAHA.115.002302.
5. Asschenfeldt B, Evald L, Heiberg J, Salvig C, Østergaard L, Dalby RB, Eskildsen SF, Hjortdal VE. Neuropsychological status and structural brain imaging in adults with simple congenital heart defects closed in childhood. J Am Heart Assoc. 2020;9:e015843. DOI: 10.1161/ JAH.120.015843.
6. Goldberg CS, Lu M, Sleeper LA, Mahle WT, Gaynor JW, Williams IA, Mussatto KA, Ohye RG, Graham EM, Frank DJ, et al. Factors associated with neurodevelopment for children with single ventricle lesions. J Pediatr. 2014;165:490–496.e8.
7. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics. 2015;135:816–825.
8. Mahle WT, Tavani F, Zimmerman RA, Nicolson SC, Galli KK, Gaynor JW, Clancy RR, Montenegro LM, Spray TL, Chiavacci RM, et al. An MRI study of neurological injury before and after congenital heart surgery. Circulation. 2002;106:1109–1114.
9. Miller SP, McCullien PS, Hamrick S, Xu D, G lidsen OW, Charlton N, Karl T, Azakia A, Ferrisero DM, Barkovich AJ, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med. 2007;357:1928–1938.
10. Limperopoulos C, Tworetsky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, Guizard N, McGrath E, Geva J, Annesse D, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation. 2010;121:26–33.
11. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetsky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, et al. Delayed cortical development in fetuses with complex congenital heart disease. Cereb Cortex. 2013;23:2932–2943. DOI: 10.1093/cercor/bhs281.
12. Ortinau OM, Mangin-Heimos K, Moen J, Alexopoulos D, Inder TE, Gholipour A, Shimony JS, Egheslady P, Schlaaggr BL, Snyder CD. Prenatal to postnatal trajectory of brain growth in complex congenital heart disease. Neuroimage Clin. 2018;20:913–922. DOI: 10.1016/j. nici.2018.09.029.
13. Kochunov P, Glahn DC, Fox PT, Lancaster JL, Saleem K, Shelledy W, Zilles K, Thompson PM, Coulon O, Margin JF, et al. Genetics of primary cerebral gyriofication: heritability of length, depth and area of primary sulci in an extended pedigree of Papio baboons. Neuroimage. 2010;53:1126–1134. DOI: 10.1016/j. neuroimage.2009.12.045.
14. Kostovic I, Vasung L. Insights from in vitro fetal magnetic resonance imaging of cerebral development. Semin Perinatol. 2009;33:220–233.
15. Kroenke CD, Bayly PV. How forces fold the cerebral cortex. J Neurosci. 2018;38:767–775. DOI: 10.1523/JNEUROSCI.1105-17.2017.
16. Zhang Y, Inder TE, Neal JJ, Dierker DL, Alexopoulos D, Anderson PJ, Van Essen DC. Cortical structural abnormalities in very preterm children at 7 years of age. Neuroimage. 2015;109:469–479. DOI: 10.1016/j. neuroimage.2015.01.005.

Supplementary Material

Tables S1–S2
Abnormal Sulcal Patterns in Simple CHD

18. Sun L, Macgowan CK, Sled JG, Yoo S-J, Manlhiot C, Porayette P, Grosse-Wortmann L, Jäggi E, McCrindle BW, Kingdom J, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015;131:1313–1323. DOI: 10.1161/CIRCULATIONAHA.114.013051.

19. Lauridsen MH, Uldbjerg N, Henriksen TB, Petersen OB, Staatsbol-Gran B, Matthiesen NB, Peters D, Ringgaard S, Hjortdal VE. Cerebral oxygenation measurements by magnetic resonance imaging in fetuses with and without heart defects. Circ Cardiovasc Imaging. 2017;10:e006459. DOI: 10.1161/CIRCIMAGING.117.006459.

20. Morton SU, Maleyeff L, Wypij D, Yun HJ, Newburger JW, Bellinger DC, Asschenfeldt et al. Abnormal Sulcal Patterns in Simple CHD. J Am Heart Assoc. 2021;10:e018580. DOI: 10.1161/JAHA.120.018580

21. Dubois J, Benders M, Borradori-Tolisa C, Cachia A, Lazeyras F, Ha-Vinh Leuchter R, Sizonenko SV, Warfield SK, Mangin JF, Hüppi PS. Primary cortical folding in the human newborn: an early marker of later functional development. Brain. 2008;131:2028–2041. DOI: 10.1093/brain/awn137.

22. Sun L, Macgowan CK, Sled JG, Yoo S-J, Manlhiot C, Porayette P, Grosse-Wortmann L, Jäggi E, McCrindle BW, Kingdom J, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015;131:1313–1323. DOI: 10.1161/CIRCULATIONAHA.114.013051.

23. Blanton RE, Levitt JG, Thompson PM, Narr KL, Capetillo-Cuniflè L, Nobel A, Singerman JD, McCracken JT, Toga AV. Mapping cortical asymmetry and complexity patterns in normal children. Psychiatry Res. 2001;107:29–43. DOI: 10.1016/S0925-4927(01)00091-9.

24. Ortinau C, Alexopoulos D, Dierker D, Van Essen D, Beca J, Inder T. Cortical folding is altered before surgery in infants with congenital heart disease. J Pediatr. 2013;163:1507–1510. DOI: 10.1016/j.jpeds.2013.06.045.

25. Watkins KE. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Circulation 2001;11:868–877. DOI: 10.1093/circulation/11.9.868.

26. Eskildsen SF, Østergaard LR. Quantitative comparison of two cortical surface extraction methods. Comput Assist Interv Med Image Anal. 2004;8:311–323. DOI: 10.1016/j.menu.2004.06.005.

27. Robbins S, Evans AC, Collins DL, Whitesides S. Tuning and comparing spatial normalization methods. Med Image Anal. 2004;8:311–323. DOI: 10.1016/j.media.2004.06.005.

28. Lyttelton O, Boucher M, Robbins S, Evans A. An unbiased iterative group registration template for cortical surface analysis. Neuroimage. 2007;34:1535–1544. DOI: 10.1016/j.neuroimage.2006.10.041.

29. Yun HJ, Vasung L, Tarui T, Rollins CK, Ortinau CM, Grant PE, Im K. Temporal patterns of emergence and spatial distribution of sulcal pits during fetal life. Cereb Cortex. 2020;30:4257–4268. DOI: 10.1093/cercor/bhu305.

30. Boucher M, Whitesides S, Evans A. Depth potential function for folding pattern representation, registration and analysis. Med Image Anal. 2009;13:203–214. DOI: 10.1016/j.media.2008.09.001.

31. Chung MK, Worsley KJ, Robbins S, Paus T, Taylor J, Giedd JN, Rapoport JL, Evans AC. Deformation-based surface morphometry applied to gray matter deformation. Neuroimage. 2003;18:198–213. DOI: 10.1016/S1053-8119(02)00174-4.

32. Im K, Ho JH, Mangin JF, Evans AC, Kim SI, Lee JM. Spatial distribution of deep sulcal landmarks and hemispherical asymmetry on the cortical surface. Cereb Cortex. 2010;20:602–611. DOI: 10.1093/cercor/bhp127.

33. Im K, Rasche NM, Smith SA, Ellen Grant P, Gaab N. Atypical sulcal pattern in children with developmental dyslexia and at-risk kindergarteners. Cereb Cortex. 2016;26:1138–1148. DOI: 10.1093/cercor/bhu085.

34. Leordeanu M, Hebert M. A spectral technique for correspondence problems using pairwise constraints. In: Proceedings of the IEEE International Conference on Computer Vision. New York, NY:IEEE;2005 :1482–1489.

35. Watkins KE. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Circulation 2001;11:868–877. DOI: 10.1093/circulation/11.9.868.

36. Blanton RE, Levitt JG, Thompson PM, Narr KL, Capetillo-Cuniflè L, Nobel A, Singerman JD, McCracken JT, Toga AV. Mapping cortical asymmetry and complexity patterns in normal children. Psychiatry Res. 2001;107:29–43. DOI: 10.1016/S0925-4927(01)00091-9.

37. Ortinau C, Alexopoulos D, Dierker D, Van Essen D, Beca J, Inder T. Cortical folding is altered before surgery in infants with congenital heart disease. J Pediatr. 2013;163:1507–1510. DOI: 10.1016/j.jpeds.2013.06.045.

38. Wagenerfuhr L, Meyer AK, Marrone L, Storch A. Oxygen tension within the neurogenic niche regulates dopaminergic neurogenesis in the developing midbrain. Stem Cells Dev. 2016;25:227–238. DOI: 10.1098/scd.2015.0214.

39. Zhao T, Zhang CP, Liu ZH, Wu LY, Huang X, Wu HT, Xiong L, Wang X, Wang YM, Zhu LL, et al. Hypoxia-driven proliferation of embryonic neural stem/progenitor cells—role of hypoxia-inducible transcription factor-1α. FEBS J. 2008;275:1824–1834.

40. Giussani DA. The fetal brain sparing response to hypoxia: physiological mechanisms. J Physiol. 2016;594:1215–1230. DOI: 10.1113/jphysiol.2015.128053.

41. Elleses SG, Workman CT, Bouvagnet P, Loffredo CA, McBride KL, Hinton RB, van Engelen K, Gertsen EC, Mulder BJM, Postma AV, et al. Familial co-occurrence of congenital heart defects follows distinct patterns. Eur Heart J. 2018;39:1015–1022. DOI: 10.1093/eurheartj/ehx314.

42. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, DePalma SR, McKean D, Wakimoto H, Gorham J, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. Science. 2015;350:1262–1266. DOI: 10.1126/science.aac3986.

43. Nyboe C, Olesen MS, Nielsen-Kudsk JE, Hjortdal VE. Atrial fibrillation and stroke in adult patients with atrial septal defect and the long-term effect of closure. Heart. 2015;101:706–711. DOI: 10.1136/heartjnl-2014-306552.

44. Karunanithi Z, Nyboe C, Hjortdal VE. Long-term risk of atrial fibrillation and stroke in patients with atrial septal defect diagnosed in childhood. Am J Cardiol. 2017;119:461–465. DOI: 10.1016/j.amjcard.2016.10.015.

45. Larsen SH, Olesen M, Emmertsen K, Hjortdal VE. Interventional treatment of patients with congenital heart disease. J Am Coll Cardiol. 2017;69:2725–2732.

46. Nyboe C, Karunanithi Z, Nielsen-Kudsk JE, Hjortdal VE. Long-term mortality in patients with atrial septal defect: a nationwide cohort-study. Eur Heart J. 2018;39:993–998. DOI: 10.1093/eurheartj/ehx687.

47. Nyboe C, Fonager K, Larsen ML, Andreasen J; Lundbye-Christensen S, Hjortdal V. Effect of atrial septal defect in adults on work participation (from a nation wide register-based follow-up study regarding work participation and use of permanent social security benefits). Am J Cardiol. 2019;124:1775–1779. DOI: 10.1016/j.amjcard.2019.08.041.

48. Nyboe C, Uthemlom S, Larsen SH, Rask C, Redington A, Hjortdal V. Risk of lifetime psychiatric morbidity in adults with atrial septal defect (from a nation-wide cohort). Am J Cardiol. 2020;128:1–6. DOI: 10.1016/j.amjcar.d.2020.04.047.
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 |
| Sulcal Region               | Mean ± SD  | Lower Bound ± SD | Upper Bound ± SD | Lower Depth ± SD | Upper Depth ± SD |
|----------------------------|------------|------------------|------------------|-----------------|-----------------|
| Inferior temporal sulcus   | 0.3492 ± 0.3976 ± 0.3303 ± 0.570 ± 0.063 | 0.1566 ± 0.1716 ± 0.1187 | 0.1050 ± 0.0796 ± 0.0487 ± 0.178 ± 0.536 | 0.1958 ± 0.2532 ± 0.1488 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |
| Occipito-temporal sulcus   | 0.0068 ± 0.0159 ± 0.0959 ± 0.001* ± 0.007* | 0.1139 ± 0.1339 ± 0.1022 | 0.7512 ± 0.6970 ± 0.6978 ± 0.291 ± 0.987 | 0.1985 ± 0.1637 ± 0.2193 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |
| Collateral sulcus          | -0.8529 ± -0.8823 ± -0.8332 ± 0.284 ± 0.033* | 0.0672 ± 0.1016 ± 0.0827 | 0.5578 ± 0.5390 ± 0.4982 ± 0.070 ± 0.289 | 0.1255 ± 0.1691 ± 0.1430 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |
| Orbital sulcus             | 0.4808 ± 0.4481 ± 0.4819 ± 0.979 ± 0.394 | 0.1841 ± 0.1370 ± 0.1772 | 0.5578 ± 0.5390 ± 0.4982 ± 0.070 ± 0.289 | 0.1255 ± 0.1691 ± 0.1430 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |
| Olfactory sulcus           | -0.6494 ± -0.6831 ± -0.5930 ± 0.216 ± 0.032* | 0.2065 ± 0.1598 ± 0.1730 | 0.5578 ± 0.5390 ± 0.4982 ± 0.070 ± 0.289 | 0.1255 ± 0.1691 ± 0.1430 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |
| Cingulate sulcus           | -0.5464 ± -0.5773 ± -0.5703 ± 0.473 ± 0.842 | 0.1597 ± 0.1706 ± 0.1159 | 0.5578 ± 0.5390 ± 0.4982 ± 0.070 ± 0.289 | 0.1255 ± 0.1691 ± 0.1430 | 0.1349 ± 0.0949 ± 0.0920 ± 0.194 ± 0.925 |

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.

| 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  |
|                       | 0.000 | -0.000012 | 0.000173 | -0.07 | 0.946 |
|-----------------------|-------|-----------|----------|-------|-------|
| Immediate Recall      | 0.003 | -0.000065 | 0.000213 | -0.31 | 0.761 |
| Delayed Recall        | 0.012 | 0.003875  | 0.006311 | 0.61  | 0.544 |
| Recognition           | 0.003 | 0.000007  | 0.000065 | 0.008 | 0.939 |
| Total Learning        | 0.001 | 0.000044  | 0.000222 | 0.20  | 0.845 |
| Delayed Recall        | 0.092 | 0.012183  | 0.006868 | 1.77  | 0.086 |
| Recognition           | 0.008 | -0.000114 | 0.00022  | -0.51 | 0.614 |

**Auditory learning and memory**

|                       | 0.000 | 0.000017  | 0.000210 | 0.08  | 0.939 |
|-----------------------|-------|-----------|----------|-------|-------|
| Trial 1               | 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 $R^2$, $B \pm$ 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.