Altered Cortical Folding Depth in Fetuses with Down Syndrome

Hyuk Jin Yun[1], Juan Perez[1], Neel Madan[2], Rie Kitano[3], Shizuko Akiyama[4], Diana W. Bianchi[5], P. Ellen Grant[1], Tomo Tarui[4*], and Kiho Im[1*]

[1]Fetal Neonatal Neuroimaging and Developmental Science Center, Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.
[2]Department of Radiology, Tufts Medical Center, Boston, MA, USA.
[3]Obstetrics and Gynecology, Long Island Jewish Medical Center, New Hyde Park, NY, USA.
[4]Mother Infant Research Institute, Tufts Medical Center, Boston, MA, USA.
[5]Prenatal Genomics and Fetal Therapy Section, Medical Genetics Branch, National Human Genome Research Institute, Bethesda, MD, USA.

FNNDSC

Introduction

- Brain abnormalities in Down Syndrome (DS) are considered to originate from early fetal life with ***decreased neurogenesis and abnormal neuronal proliferation***.
- Affected by neurogenesis, ***cortical folding is an important marker of neurodevelopment*** and its regional pattern is thought to be associated with the development of specific functional areas.
- Therefore, regional analysis of cortical folding in fetuses with DS may provide better understandings of ***early brain abnormalities***, and ***specific neurocognitive impairments*** caused by DS.
- In this study, we compared ***regional differences of depth between fetuses with DS and TD fetuses***.

Methods

Data and magnetic resonance image (MRI) processing

- The study was approved by the local Institutional Review Board at Boston Children's Hospital and Tufts Medical Center.
- Nine fetuses with DS and 17 typically developing (TD) fetuses were included in this study (Table 1).

Table 1. Demographic information of the groups

	GW (mean ± SD)	Sex (male/female)
DS (n=9)	29.1 ± 4.2	4/5
TD (n=17)	28.4 ± 3.4	7/10

GW: gestational week, SD: standard deviation. Between the DS and TD groups, there are no significant differences in GW (p = 0.650) and sex ratio (p = 0.952).

- From T2-weighted brain MRIs, we adopted our fetal brain MRI processing pipeline (Yun et al., 2019, 2020). We (1) created a motion-corrected 3D fetal brain volume using a slice to volume registration; (2) segmented cortical plate from the 3D volume using a semi-automatic approach; and (3) extracted cortical plate surface.
- The surface was aligned to a fetal template surface using a 2D sphere-to-sphere warping for vertex-wise correspondence (Yun et al., 2019).
- On the aligned surface, sulcal depth was calculated by Adaptive Distance Transform (Yun et al., 2013) which searches shortest path from the convex hull following the sulcal shape (Figure 1).

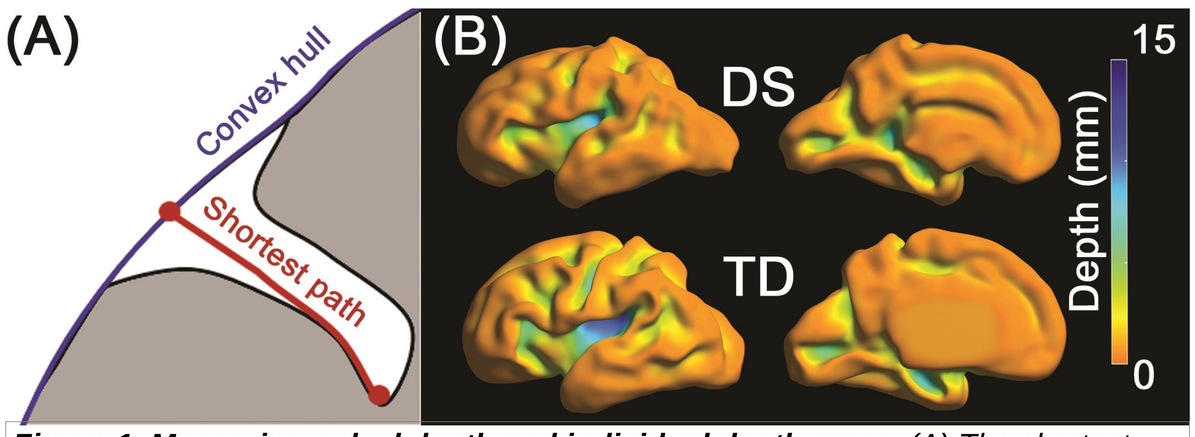

Figure 1. Measuring sulcal depth and individual depth maps. *(A) The shortest path between convex hull and a vertex of the cortical surface. (B) sulcal depth maps of a fetus with DS and a TD fetus.*

Statistical analysis

- To assess regional group differences, we employed a general linear model with controlling for GW at each vertex of cortical plate surfaces.
- False discovery rate (FDR) correction was applied to correct multiple comparisons problem.

Results and Conclusion

- Fetuses with DS showed significantly shallower sulcal depth compared to TD fetuses in the bilateral Sylvian fissure, right central, and parieto-occipital sulci (Figure 2).
- In contrast to others, a region belonging to the left superior temporal sulcus showed significantly deeper sulcal depth in fetuses with DS compared to TD fetuses (Figure 2).

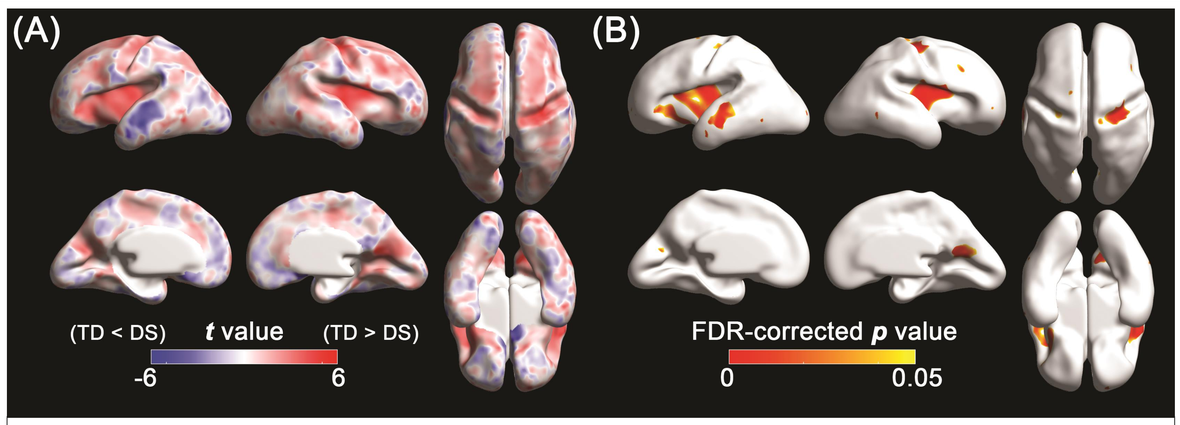

Figure 2. Statistical results of the vertex-wise comparison in sulcal depth between DS and TD fetuses. *(A) Statistical t map. (B) FDR-corrected p map.*

- To assess the regional differences in age-related trajectory of sulcal depth between DS and TD groups, we segmented the cortical regions in which significant group difference in sulcal depth was found (Figure 3A).
- In each clustered region, average sulcal depth were obtained to generate age-related depth changes. In all the clusters, sulcal depth difference between the two groups was gradually increased as gestation progressed (Figure 3B).

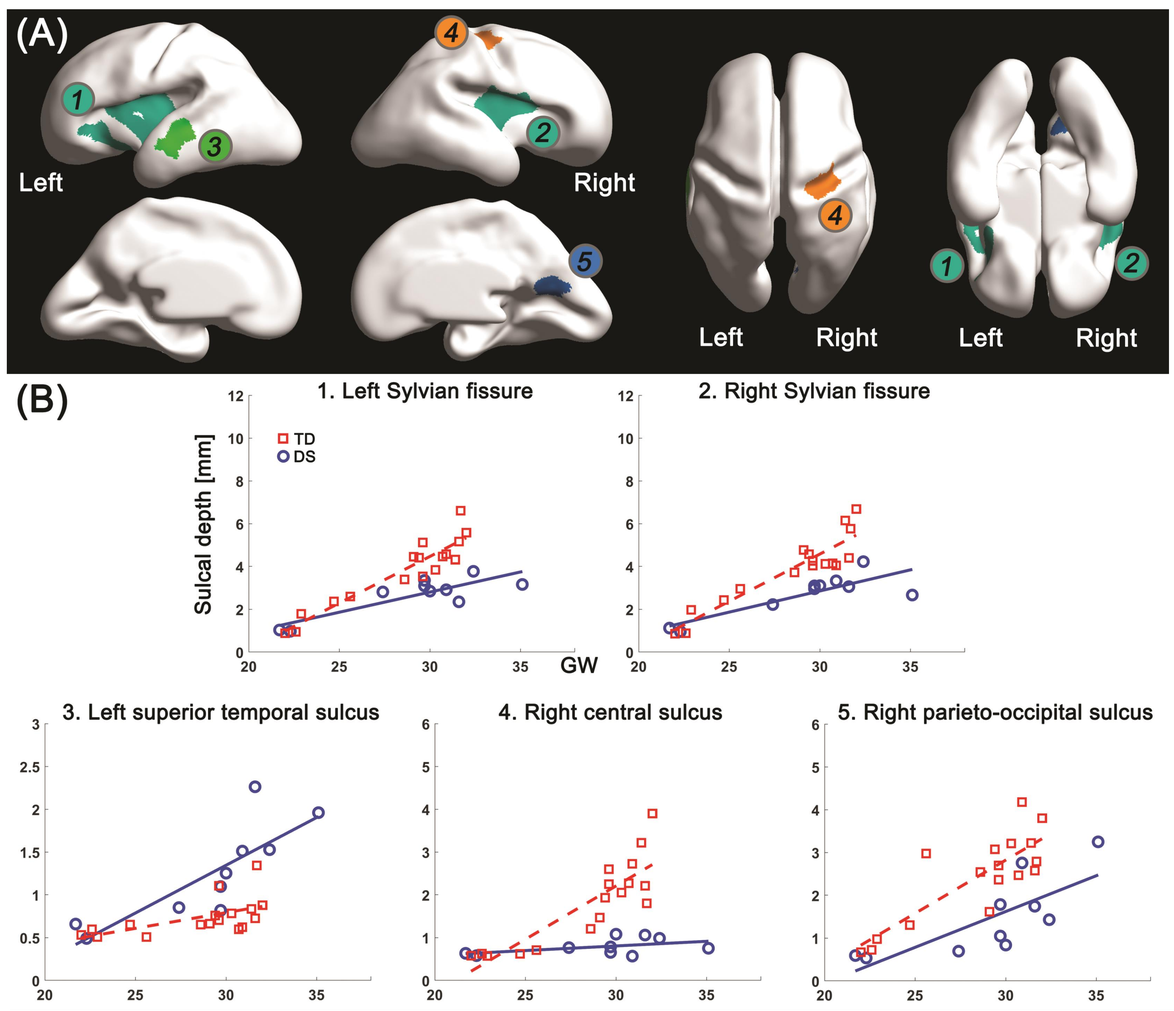

Figure 3. Clustered regions showing significant group difference in sulcal depth and their age-related trajectories of sulcal depth. *(A) Clustered regions. (B) Growth trajectories of average sulcal depth in the clusters.*

- Shallow sulcal depth in the Sylvian fissure is supported by abnormal development in the Sylvian fissure of children with DS.
- Findings in the right central sulcus may be associated with the motor abnormalities in DS that have been reported in several studies
- Shallow sulcal depth in the right parieto-occipital sulcus is consistent with gray matter reduction in medial part of occipital lobe in DS.
- Deeper sulcal depth in left superior temporal sulcus may be related to atypical asymmetry caused by impairments of language function in DS.
- Our findings demonstrated that ***investigating cortical folding in the fetal brain with DS is a useful tool to detect altered brain development and pathology in early fetal life***.

References

Guidi et al., 2018, Brain Pathol., vol. 28, no. 6, pp. 986–998
Tarui et al., 2020, Cereb Cortex, 30:382–390
Yun et al., 2013, PLOS ONE, 8:e55977
Yun et al., 2019, Neuroimage, 188, 473-482
Yun et al., 2020, Cereb Cortex, 30:4257–4268

Fetal-Neonatal Neuroimaging and Developmental Science Center (FNNDSC) **Hyuk Jin Yun (HyukJin.Yun@childrens.harvard.edu)**