# Spatiotemporal Patterns of Sulcal Pits in Early Fetal Life

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## Introduction

- Sulcal pits are thought to represent the first cortical folds of primary sulci, and their spatial distribution is uniform across individuals.
- The uniform spatial distribution has been hypothesized to be ***predetermined in early fetal stages*** under genetic controls, thus it may contain ***initial information of human brain development.***
- To enhance our understandings of early brain development, it is ***necessary to investigate pit distribution in the fetal brain***.
- Furthermore, in typically developing (TD) fetuses, each cortical sulcus emerges in a specific timing which might be ***affected by rapid growth and regional expansion of brain functional areas***.
- Associated with subdivisions of functional areas, quantifying the timetable of pit emergence may provide more ***regional information of functional localization*** in human brain development.
- In this study, we quantified and analyzed (1) ***spatial pit distribution*** and (2) ***the timing of pit emergence*** using TD fetuses.

## Methods

### *Data and image processing*

- The study was approved by the local Institutional Review Board at Boston Children's Hospital and Tufts Medical Center.
- A total of 48 TD fetuses ranged from 22.0 to 32.0 gestational week (GW) were included and divided into 3 subgroups by GW (Table 1).

**Table 1. Demographic information of the fetuses**

| | GW (mean ± standard deviation [SD]) | Sex (male/female) |
|---|---|---|
| **All (n=48)** | 26.7 ± 2.9 | 30/18 |
| **G*early* (n=16)** | 23.5 ± 0.8 | 10/6 |
| **G*mid* (n=16)** | 26.6 ± 0.9 | 10/6 |
| **G*late* (n=16)** | 30.1 ± 1.0 | 10/6 |

- Using our fetal brain magnetic resonance image (MRI) processing pipeline, we extracted cortical plate surfaces. The surfaces were aligned to a fetal template for vertex correspondence, and sulcal pits were extracted on the aligned surfaces (Yun et al, 2019, 2020).
- To define consistent regions of sulcal pits across individuals, we generated density and cluster maps of sulcal pits (Yun et al., 2020).
- Individual sulcal pits were smoothed and averaged in the template to generate density map (Figure 1A). High density indicated that the sulcal pits were extracted in many subjects with small spatial variation.
- Clusters with high density were segmented using same criteria of pit extraction (Figure 1B). A total of 76 clusters were segmented.

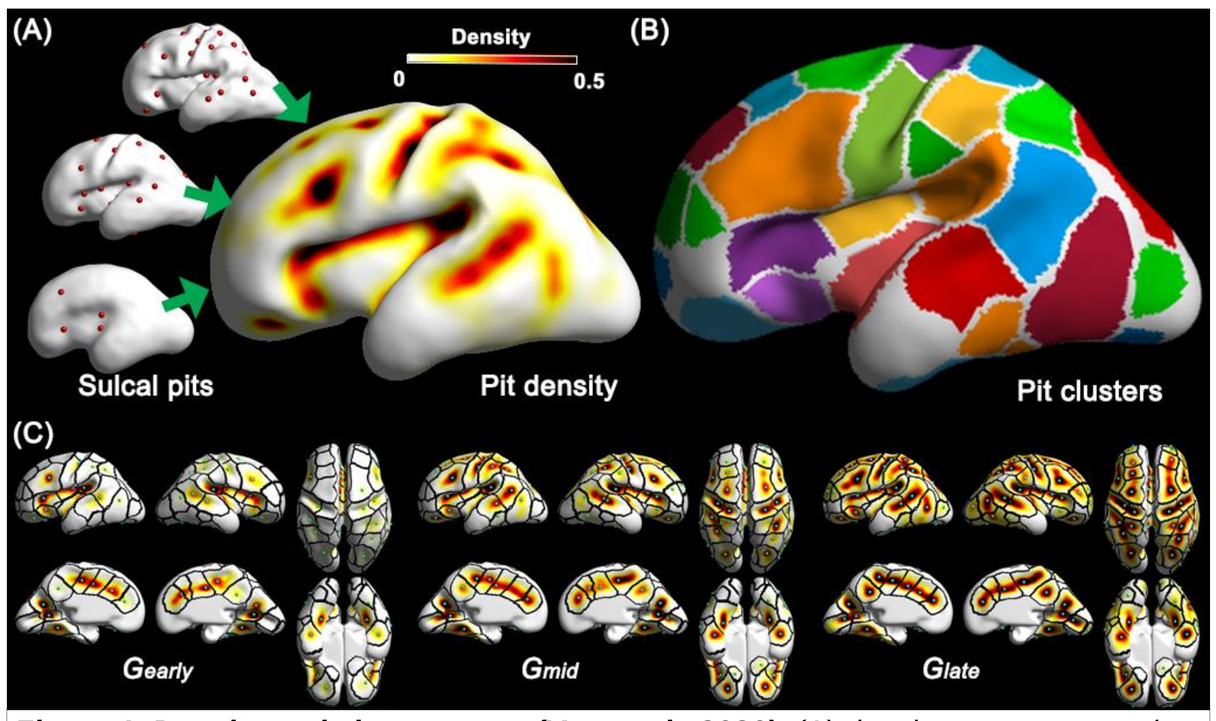


***Figure 1. Density and cluster maps (Yun et al., 2020).*** *(A) density map generated from all the fetuses. (B) cluster map. (C) density maps of subgroups. Back lines indicate the boundary of the clusters. Light blue spheres indicate the position of peak density in each cluster. While density values vary, its pattern and peak positions in clusters are similar across subgroups.*

### ***(1) Spatial distribution of sulcal pits***

- We converted 3D pit coordinates to 1D (Figure 2).
- In each cluster, we performed a Kruskal-Wallis test to investigate the difference in the position of 1D coordinate among the subgroups.
- Similarity of the spatial variance of sulcal pits across the subgroups were also tested by Pearson's correlation with SD of the 1D coordinates.

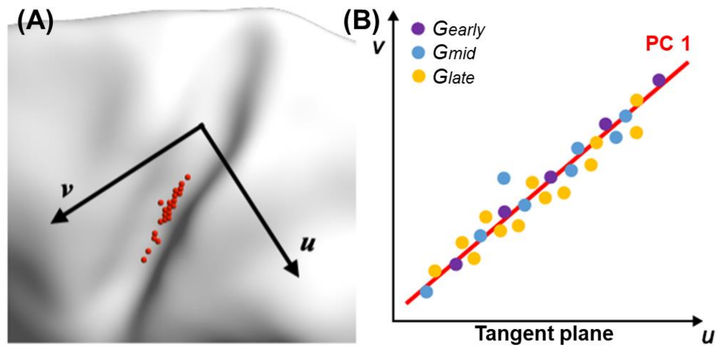


***Figure 2. Sulcal pit distribution in a cluster.*** *(A) sulcal pits (red spheres) on the template. (B) sulcal pits (colored circles) projected onto a 2D tangential plane. Along the first principal component (PC1, red line)1D pit coordinates were calculated (Yun et al., 2020).*

### ***(2) Timing of emergence of sulcal pits***

- To estimate the timing of pit emergence, we generated crosstab table with the presence of sulcal pits and performed chi-square tests to examine if there is a rapid change of pit presence between G*early* and G*mid* and between G*mid* and G*late*.
- The significant change between the subgroups indicates that there is a specific timing of emergence of sulcal pits.
- False discovery rate (FDR) correction were performed in all the analysis.

## Results and Conclusion

- Density maps of subgroups were generated (Figure 1C). The patterns of density among subgroups were similar to each other.
- In all clusters, the Kruskal-Wallis test showed ***no significant difference in pit position among the groups*** (FDR corrected p> 0.05). ***Significant correlation of SD of sulcal pit*** across fetal brains were found between G*early* and G*mid* (r= 0.59 and p< 0.001), G*early* and G*late* (r= 0.50 and p= 0.001), and G*mid* and G*late* (r= 0.70 and p < 0.001).
- We obtained ***three regionally different timings of pit emergence across clusters*** (Figure 3) : (1) high pit presence rate (>0.3) in G*early*, (2) increase of pit presence between G*early* and G*mid*, and (3) emerging in later fetal life.

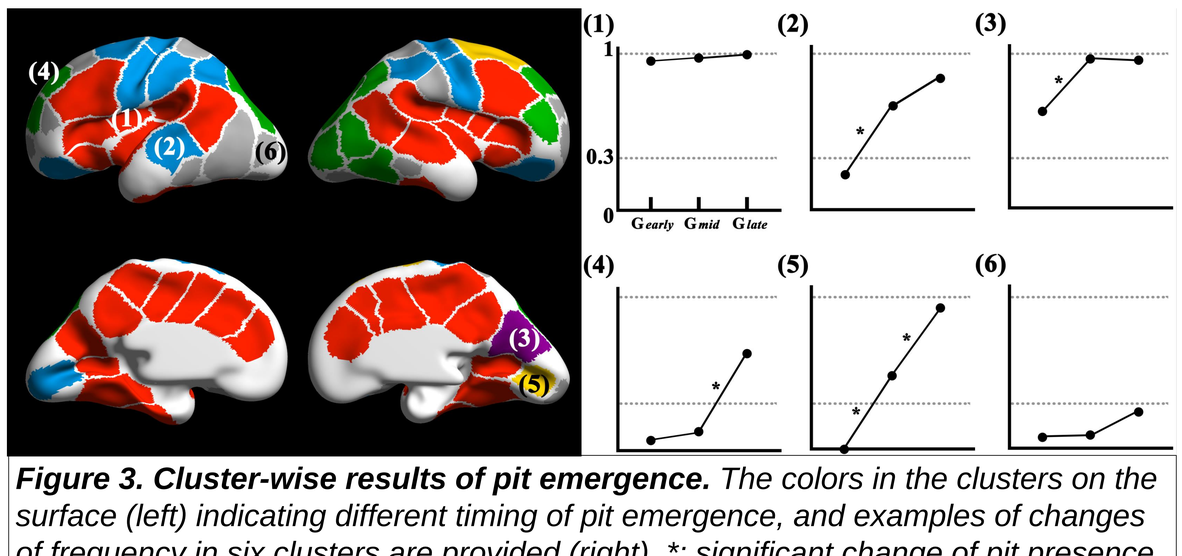


***Figure 3. Cluster-wise results of pit emergence.*** *The colors in the clusters on the surface (left) indicating different timing of pit emergence, and examples of changes of frequency in six clusters are provided (right). *: significant change of pit presence (FDR corrected p < 0.05) between two subgroups. (Yun et al., 2020).*

- Temporally invariant position and similar spatial variance indicate that sulcal pits ***represent maintain spatial distribution of the first folds***.
- The gradient of timing of cortical maturation from the central to peripheral regions ***reflects development of brain functional areas***.
- Finally, our findings demonstrate that sulcal pits are ***life-long anatomical landmarks from the initial stage of human brain development and functional localization***.

## References

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