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Aberrant cortical thickness and gyrification are linked to synaptic organization in preterm adults

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Introduction

Interruption of normal brain development due to preterm birth can entail altered cortical architecture development with aberrations not only in neonates and infants [1] but also in adolescents and adults [2-4]. Even though magnetic resonance imaging (MRI) studies have contributed important work to the understanding of these changes and their possible mechanistic basis, cell biological underpinnings remain largely unidentified. Imaging transcriptomics addresses this issue by using cross-sample spatial correlation as a proxy for similarity between cortical morphology and regional gene expression. Thus, we investigated cellular underpinnings of cortical thickness (CTh) and gyrification alterations in preterm adults using an imaging transcriptomic approach.

Research questions

- Are cortical thickness and local gyrification indices **significantly different** in VP/VLBW compared to FT individuals?
- **Which biological processes** could potentially underlie these aberrations?

Methods

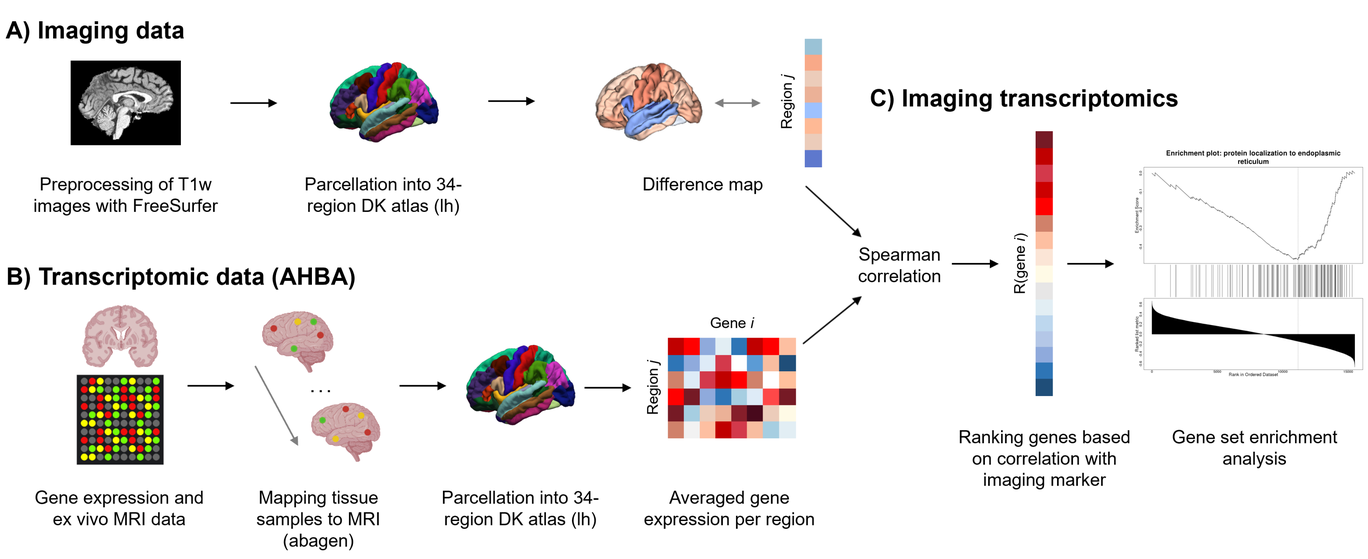

Figure 1: Imaging transcriptomics workflow. (A) Imaging data are preprocessed and parcellated into the 34-region Desikan-Killiany atlas (left hemisphere only). A difference map between groups is correlated with the preprocessed transcriptomic data (B) using cross-sample spatial Spearman correlation (C). Next, Gene Set Enrichment Analysis is conducted to retrieve biological processes. Adapted from [8].

- Cortical morphology of 91 very preterm born adults (< 32 weeks of gestation and / or born with < 1500 g body weight; VP/VLBW) and 106 full-term (FT) controls captured by MRI
- Analysis of cortical thickness (CTh) and local gyrification index (lGI) in FreeSurfer (v7.1.1)
- Investigation of CTh and lGI group differences via 2-sample t-tests, corrected for scanner and sex
- Correlation of absolute group differences of CTh and lGI and regional gene expression profiles available in the Allen Human Brain Atlas (AHBA)
- Thereby, AHBA preprocessing followed the latest standards using the abagen toolbox [5, 6]
- Explorative Gene Set Enrichment Analysis (GSEA) [7] was used to analyze enrichment for GO biological processes

Results

- Widespread reductions in CTh and lGI (Fig. 2) in the VP/VLBW cohort, mainly in temporal and parietal association cortices
- Significant associations between CTh and lGI changes after preterm birth and genes enriched for processes related to synaptic transmission and synaptic organization (Fig.3)
- Particularly glutamate receptor signaling stands out

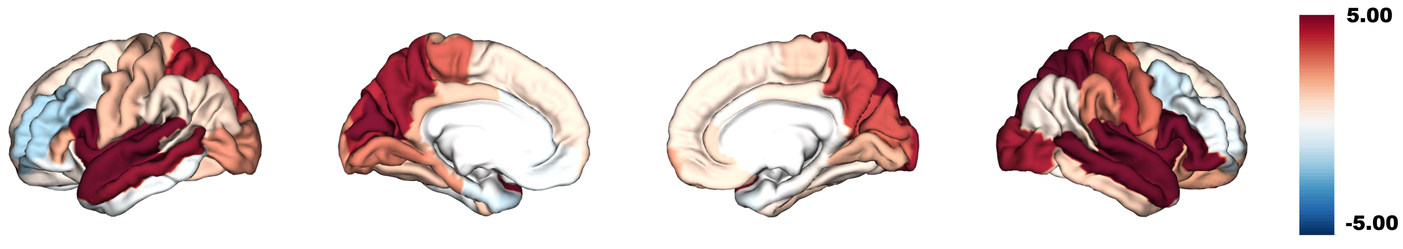

Figure 2: ROI-wise group difference in local gyrification index depicted as t-values corrected for sex and scanner. Warm colors indicate regions with lower lGI values in VP/VLBW individuals compared to FT controls.

Conclusion

- Aberrant cortical thickness and gyrification in preterm born adults are associated with synapse-relevant gene expression, especially glutamate receptor-related synapses
- In line with animal research:
  - Brain changes after prematurity correspond to abnormalities in synaptic formation and dendrite branching [9]
  - Impact of neuroinflammation during brain development on synapse structure and function [10]

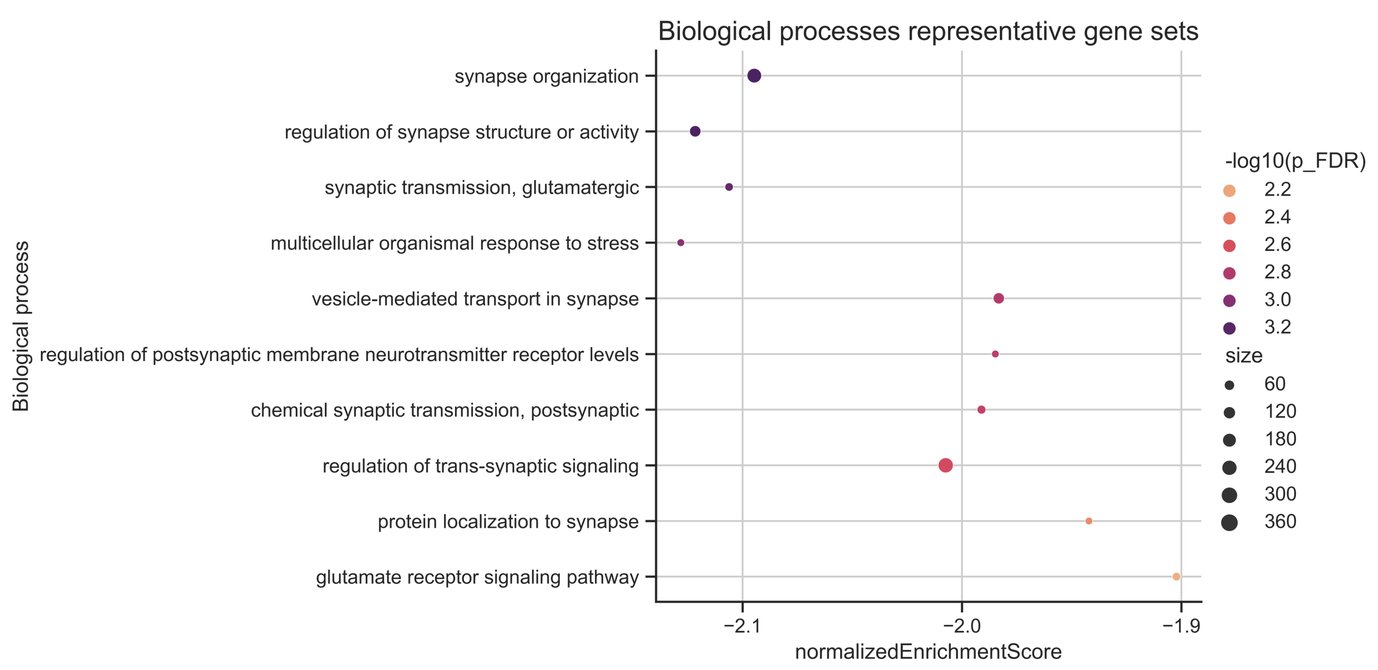

Figure 3: 10 representative GO biological processes associated with absolute group difference in lGI between FT and VP/VLBW adults. Enrichment of GO biological processes is depicted in a catplot. Dot positions represent normalized enrichment scores of the respective gene category, dot sizes represent gene set size.

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