# MRI Processing Pipeline Variability and Infant Brain Morphometry Associations to 4-Month Infant Temperament

Kayla Foster[1], Courtney Filippi[1,2], Emma Margolis[1], Sanjana Ravi[1], Maya Bracy[1], Daniel Pine[2], Nathan Fox[1]

[1]Child Development Lab, University of Maryland, College Park, MD [2]National Institute of Mental Health, Bethesda, MD

## Introduction

Negative reactive temperament, an infant temperament characterized by fear of novelty, is associated with differences in adolescent amygdala volume[1] and adult prefrontal cortex (PFC) thickness[2].

While these studies tell us about adolescent and adult brain structure, to date, it remains unclear when these patterns first arise. It is possible that these differences in brain morphometry arise during infancy at the earliest point when temperament can be measured (i.e., at age 4-months).

Evaluating this possibility is a challenge because:
(1) few tools exist for analyzing infant brain data
(2) tools that exist for infant data are optimized for neonatal brains
(3) tissue contrast in MRI scans changes over infancy

These factors increase the difficulty of properly segmenting gray and white matter in infant MRI data.

Thus, in order to assess associations between infant temperament and brain morphometry, an evaluation of available infant MRI processing pipelines is first necessary.

This study aims to examine:

1) **Which processing pipeline performs best for 4-month infant MRI data?**
2) **How does brain morphometry differ as a function of infant temperament at age 4-months?**

## Methods

**Reactivity Assessment (4 months of age; M=4 months 5 days)**

- Behavioral assessment involving presentation of novel auditory and visual stimuli to infants.
- Using a 7-point Likert scale, raters indicated the extent to which infants exhibited positive affect, negative affect, and motor responsivity during the stimuli presentations[3].

**MRI Data Acquisition (4-6 months of age; M=4 months 25 days)**

- Conducted in close proximity to reactivity visits (M=19 days).
- High-resolution structural MRI data (T1- and T2-weighted images) were acquired using a 3T Siemens Magnetom TrioTim scanner; 32 channel head coil.

**MRI Data Processing**

- Three infant MRI pipelines were used to process the 4-month MRI data and acquire estimates of amygdala and PFC volume:
  - iBEAT[4]: Developed at University of North Carolina at Chapel Hill
  - dHCP[5]: Developed in collaboration between King's College London, Imperial College London, and Oxford University
  - CIVET[6]: Developed at McGill University

- Two measures were used to evaluate the pipelines:
  - Percent pipeline failure
  - Percent useable data following Quality Control (QC) checks

Output from the pipeline that exhibited the greatest percent usable data following QC checks were used for focal analyses.

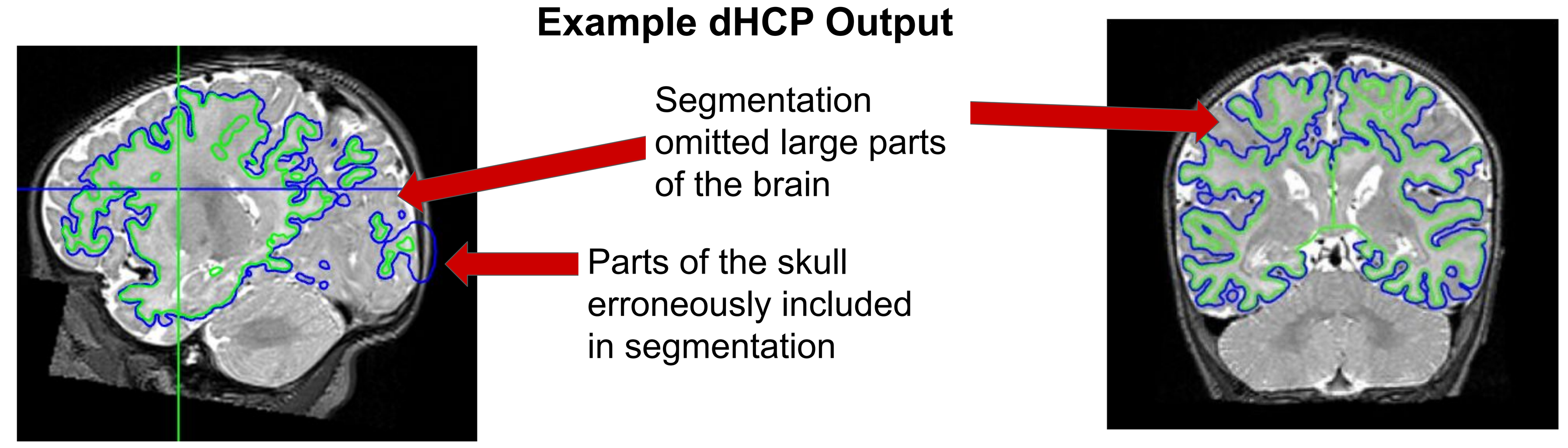
Partial correlations were used to test whether amygdala or PFC volume was associated with negative reactive temperament. These correlations controlled for total brain volume.

## Quality Control MRI Output

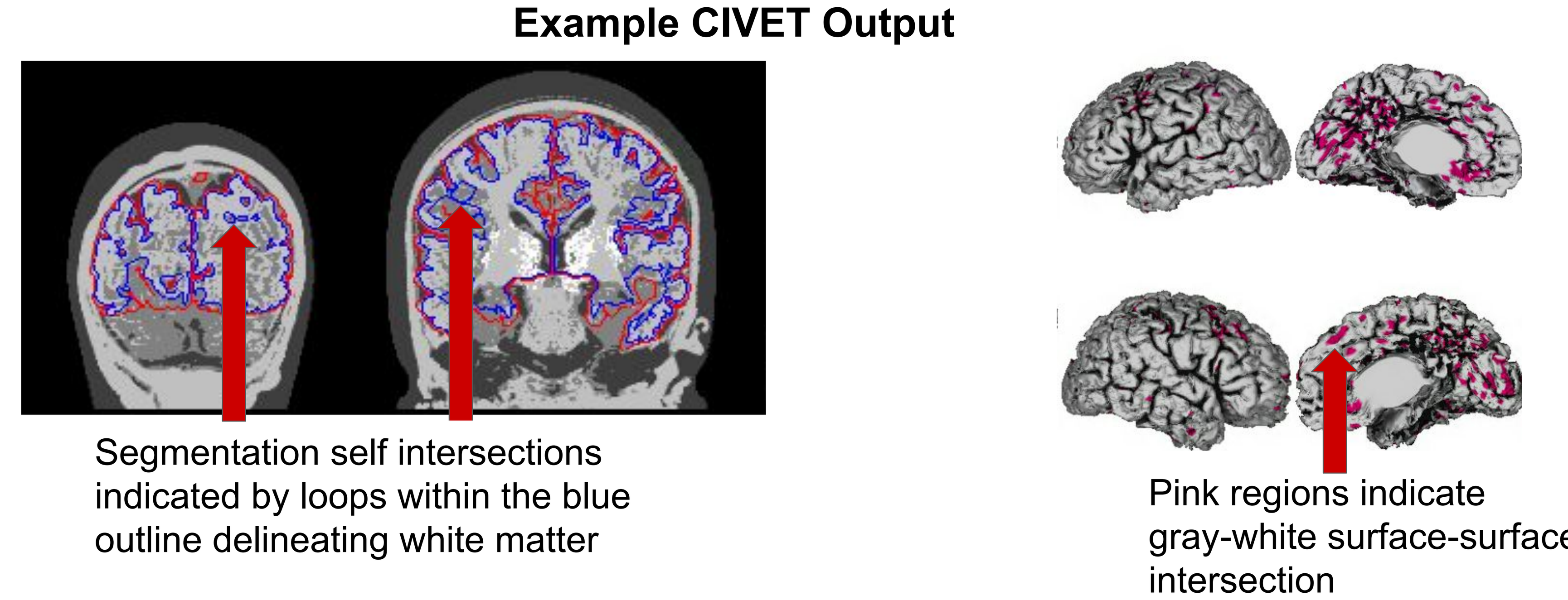
- Raters reviewed all gray and white matter segmentation and judged each segmentation as GOOD or BAD.
  - GOOD segmentations were reasonable upon visual inspection indicating relatively few errors.
  - BAD segmentations had large portions of cortex missing from the segmentation.

- Representative examples of segmentations from each pipeline are presented below.

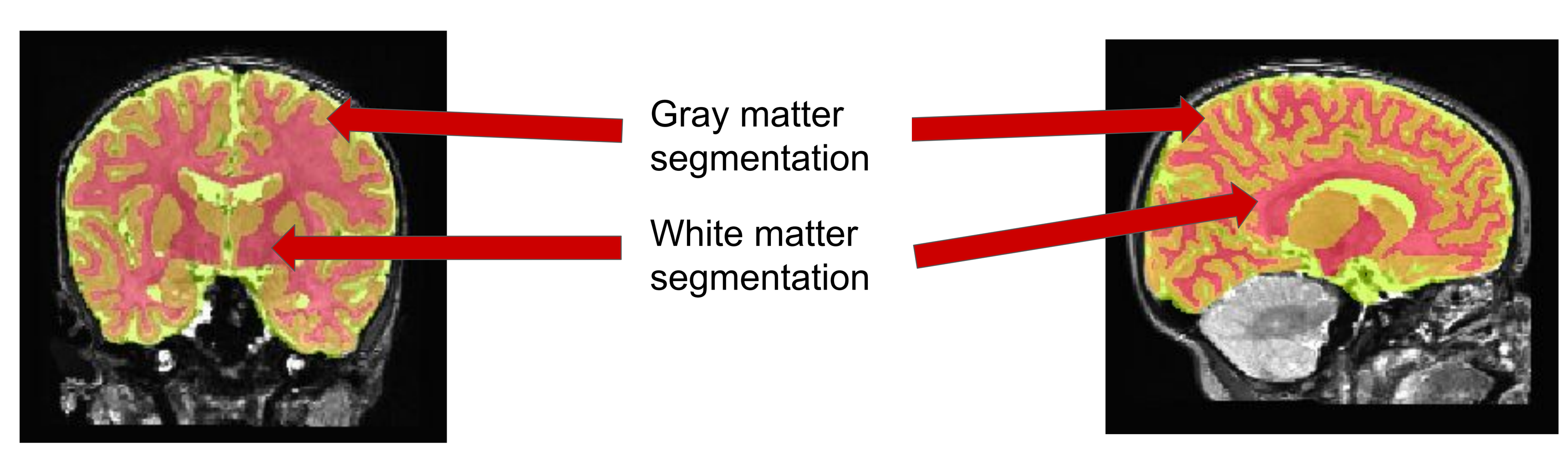
**Example dHCP Output**




**Example CIVET Output**

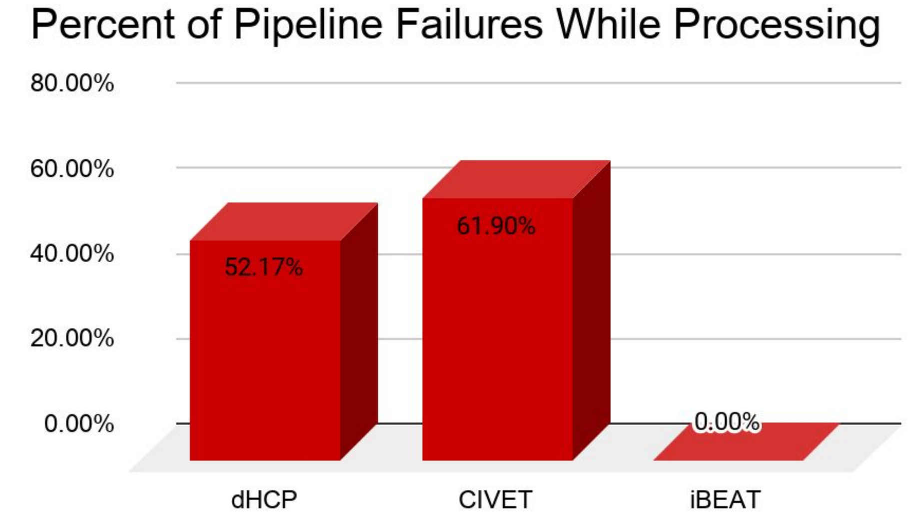



**Example iBEAT Output**

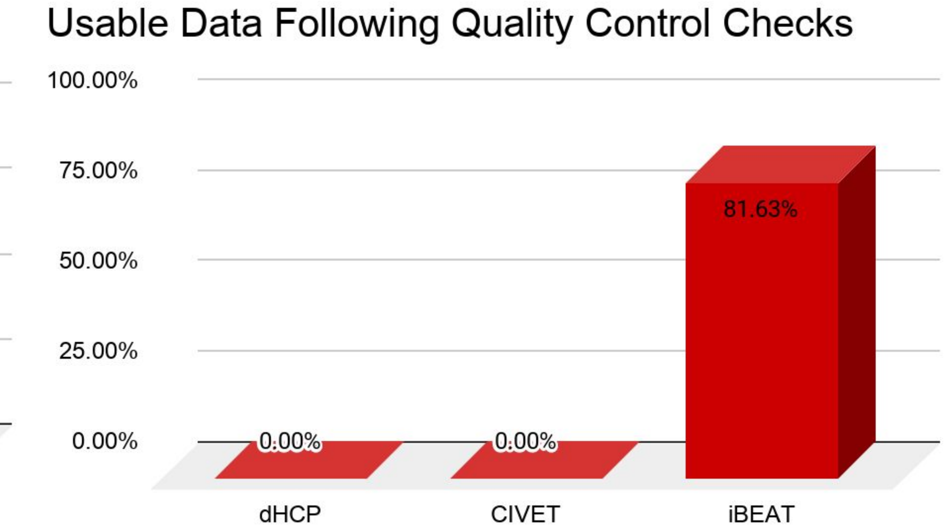



## Results

Percent of Pipeline Failures While Processing




Usable Data Following Quality Control Checks




iBEAT performed the best, with 0 pipeline failures, and about 82% good data following quality checks.

Neither amygdala volume nor PFC volume was significantly correlated with negative reactivity.

## Discussion

Summary of Findings
Results indicate that iBEAT performed the best, with no processing failures and 81.6% of the output showing good segmentations.

Comparatively, 52.1% of data failed to process when using the dHCP pipeline. 0 subjects had good segmentations. The QC checks identified large regions of the brain that were omitted from segmentation as well as non-brain regions, such as the skull, that were included in segmentation.

Similarly, 61.9% of data failed to process when using the CIVET pipeline. 0 subjects had good segmentations. QC checks indicated a large number of self-intersections which resulted in the pipeline failing to extract white matter, and the algorithm was largely unable to identify white matter.

Pipeline Similarities and Differences
These pipelines use similar methods but differ in their optimization parameters.

Similarities include: N3 correction, registration to standard space, skull-stripping, creating mask of the brain-only, tissue classification, atlas registration (and some surface generation).

The differences between the pipelines, outlined below, likely account for the disparity in success between the three processing pipelines.

**Differences Between the Pipelines**

| Pipeline | Optimization | Input Required |
|---|---|---|
| **dHCP** | • Neonate MRI data used to train algorithms | • 1 T1 image per subject |
| **CIVET** | • Adult MRI data used to train algorithms | • 1 T1 image per subject |
| **iBEAT** | • Infant MRI data from various ages used to train algorithms | • 1 T1 and T2 image per subject<br>• Age of subject<br>• Scan parameters |

Importance
These results demonstrate that QC checks on MRI data after using automated processing pipelines are crucial to ensure that outputs reasonably reflect anatomy. Segmentation errors such as leaving parts of the brain out, failing to segment white matter, and including the skull in segmentation of gray matter make it impossible to use the data for morphometry analyses.

Future Directions
- Generate continuous factor scores that represent differences across all three dimensions of reactivity (motor, positive, negative). This might better represent differences in reactivity than the negative affect dimension alone.

## References

[1]Filippi, C. A., Sachs, J. F., Phillips, D., Winkler, A., Gold, A. L., Leibenluft, E., Pine, D. S., & Fox, N. A. (2020). Infant behavioral reactivity predicts change in amygdala volume 12 years later. *Developmental Cognitive Neuroscience, 42*. https://doi.org/10.1016/j.dcn.2020.100776

[2]Schwartz, C. E., Kunwar, P. S., Greve, D. N., Moran, L. R., Viner, J. C., Covino, J. M., . . .Wallace, S. R. (2010). Structural Differences in Adult Orbital and Ventromedical Prefrontal Cortex are Predicted by 4-Month Infant Temperament. *Archives of General Psychiatry, 67*(1), 78-84. doi:10.1001/archgenpsychiatry.2009.171

[3]Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and Discontinuity of Behavioral Inhibition and Exuberance: Psychophysiological and Behavioral Influences Across the First Four Years of Life. *Society for Research in Child Development, 72*(1), 1-21. https://doi.org/10.1111/1467-8624.00262

[4]Dai, Y., Shi, F., Wang, L., Guorong, W., & Shen, D.(2013) iBEAT: A toolbox for infant brain magnetic resonance image processing. *Neuroinformatics, 11*, 211-225. https://doi.org/10.1007/s12021-012-9164-z

[5]Makropoulos, A., Robinson, E. C., Schuh, A., Wright, R., Fitzgibbon, S., Bozek, J., Counsell, S. J., Steinweg, J., Vecchiato, K., Passerat-Palmbach, J., Lenz, G., Mortari, F., Tenev, T., Duff, E. P., Bastiani, M., Cordero-Grande, L., Huges, E., Tusor, N., Tournier, J. D., … Rueckert, D. (2018). The developing human connectome project: A minimal processing pipeline for neonatal cortical surface reconstruction. *NeuroImage, 173*, 88-112. https://doi.org/10.1016/j.neuroimage.2018.01.054

[6]Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., and Evans, A.C. (2006). The CIVET Image-Processing Environment: A Fully Automated Comprehensive Pipeline for Anatomical Neuroimaging Research [Poster]. 12th Annual Meeting of the Organization for Human Brain Mapping, Florence, Italy. http://www.bic.mni.mcgill.ca/users/yaddab/Yasser-HBM2006-Poster.pdf

## Acknowledgements

Thank you to all of the families that participated in this study, everyone in the Child Development Lab, the researchers at the NIMH, and the Maryland Summer Scholars program.