INFANT BRAIN IMAGING STUDY

Quantifying Flow Dynamics of Cerebrospinal Fluid in Infants with Neurodevelopmental Disabilities Using Fréchet Regression

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Cerebrospinal Fluid (CSF) and Neurodevelopmental Disabilities (NDDs)

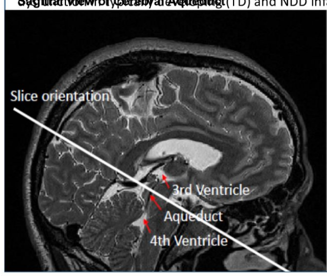
-CSF is a viscous plasma that plays a central role in maintenance of brain homeostasis. In general, CSF transfers nutrients throughout the central nervous system, removes inflammatory proteins from the lymphatic system, and protects the brain from physical trauma (Khasawneh, et al., 2018).

-CSF is produced primarily by the choroid plexus between the ventricles in the cerebral aqueduct (below) and then flows into the subarachnoid space.

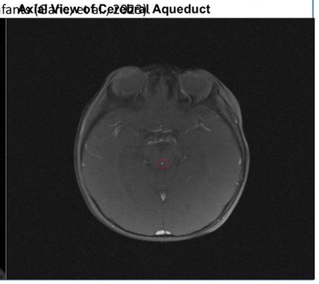
-Evidence of abnormally increased CSF volumes associated with infants who later develop Autism Spectrum Disorder (ASD) (Shen, et al., 2017). However, typical CSF volumes across developmental groups (TD and other NDDs) were relatively equal (Peterson, et al., 2023)

-Additional evidence determined potential abnormalities between CSF fluid dynamics and sleep dysfunction in typically developing (TD) and NDD infants (Garic, et al., 2023).

Sagittal View of Cerebral Aqueduct



Axial View of Cerebral Aqueduct



Fréchet Mean & Fréchet Estimation

-The Fréchet mean extends the notion of central tendency to any metric space with respect to some definition of distance. Specifically, the Fréchet mean is the expected value that minimizes the sum of the chosen distance. In the case of squared Euclidean distance, the Fréchet mean is the common mean and Fréchet variance is mean squared error. For absolute deviations, the Fréchet mean is the median.

-This concept can be extended to other metric spaces, such as use in hyperbolic space, functional space, and many non-Banach spaces.

-This definition of Fréchet estimation has been implemented in Fréchet regression (Petersen & Müller, 2019), which extends the notions of least-squares regression into novel non-Euclidean spaces. Other methods of Fréchet estimation have been proposed, such as the construction of metric covariance (Dubey & Müller, 2020), and Fréchet analysis of variance (Dubey & Müller, 2019), among others.

-Fréchet regression has been used in the analysis of sparse covariance matrices of brain myelnation (Petersen, et al., 2019) to illustrate the spatial association between T1-weighted voxel data.

$$\omega_\oplus = \underset{\omega\in\Omega}{\operatorname{argmin}}\, E(d^2(Y,\omega)), \quad V_\oplus = E(d^2(Y,\omega_\oplus))$$

Definition of Fréchet mean c/o (Petersen & Müller, 2019)

$$m_\oplus(x) = \underset{\omega\in\Omega}{\operatorname{argmin}}\, M_\oplus(\omega,x), \quad M_\oplus(\cdot,x) = E(d^2(Y,\cdot)|X=x),$$

Definition of Fréchet regression c/o (Petersen & Müller, 2019)

Temporal Associations of Velocity and Vorticity Over a Cardiac Cycle

-Use of Phase Contrast MRI to calculate the flow of CSF in the cerebral aqueduct of infants enrolled in the Infant Brain Imaging Study (IBIS), a longitudinal cohort of infants with an increased likelihood of developing Autism Spectrum Disorder. Study has multiple sites (University of Washington, University of Pennsylvania CHOP, Washington University in St. Louis, University of Minnesota, and UNC-Chapel Hill) that collect data over period of 6 to 24 months of age.

-Imaging slices taken perpendicular to flow (as seen in figures to left). Details provided in Demirel, et al. (2019).

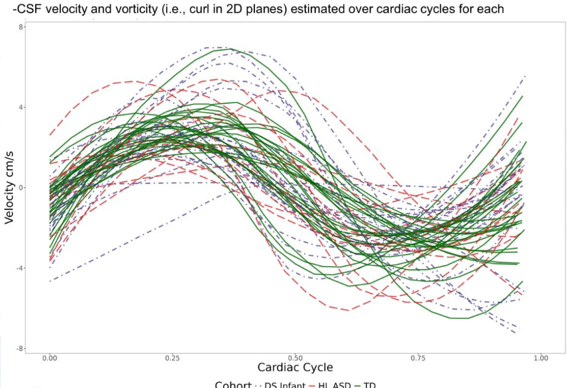
-Cardiac cycles measured using pulse oximeters, allowing for cardiac cycles to be determined automatically for each individual.

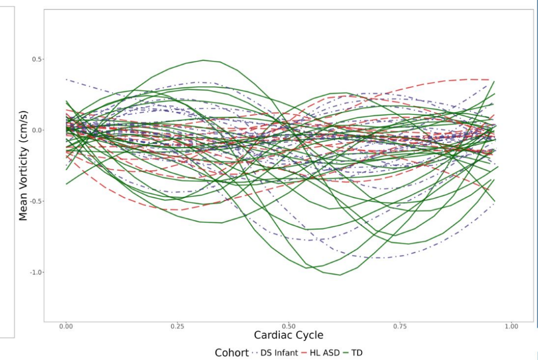
-CSF velocity and vorticity (i.e., curl in 2D planes) estimated over cardiac cycles for each

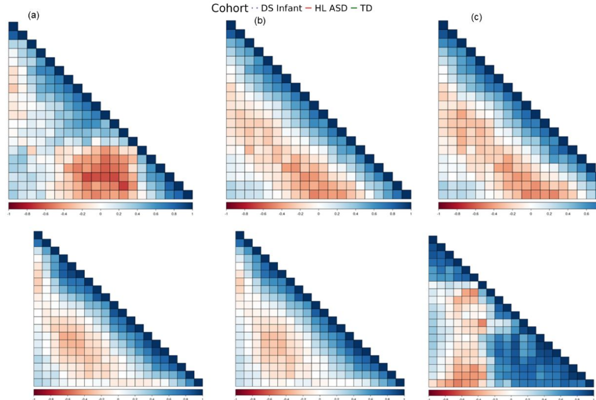
-Sample included n = 62 infants who were either typically developing (TD, n = 25), Down syndrome (DS, n = 24), or high likelihood of developing ASD (HL-ASD, n = 13).

-To account for slight variations in the cardiac cycles, local polynomial smoothing curves (loess) were estimated for the velocities and vorticities of each infant at equally spaced time intervals. These samples represented 20 PC MRI slices of the cerebral aqueduct.

-Covariance matrices for velocity and vorticity were estimated for each of the 62 infants where covariance represented the autocovariance of flow estimates over the 20 time points of the cardiac cycle.







-Top plots provide individual velocity plots (left) and vorticity plots (right) for each of the three groups. Greater velocity heterogeneity was observed for the HL ASD and DS infants than for the TD infants. This was different from the vorticity plots, which indicated more stagnant vorticity for the HL ASD and DS infants when compared to the TD infants.

-Conditional correlation matrices were estimated using Fréchet regression for the TD group (a), DS group (b), and HL ASD group (c). Velocities are shown on top and vorticities are shown on the bottom row. Greater negative correlation was seen later in the velocity cycle for TD infants, but these negative autocorrelations extended throughout the cardiac cycle for the DS and HL ASD infants.

-Conditional correlations for vorticities were different, where TD and DS infants had greater similarities. However, HL-ASD infants had greater positive autocorrelation later in the cardiac cycle.

-Using Fréchet ANOVA for covariance matrices, these differences in conditional covariances were statistically significantly different for the three groups for both velocity ($p < 0.0001$) and vorticity ($p < 0.0001$).

Discussion & Future Directions

- It's clear that the CSF flow measurements differ between these three groups, but the exact mechanisms producing these differences are unclear
- Determining the bivariate relationship of these two sets of covariance matrices would vastly improve understanding the flow mechanisms of CSF in this region
- Further, the temporal relationships have been captured well in these analyses, but certain spatial relationships have not been as well estimated. However, this region is relatively small (incorporating 9 – 12 voxels), making spatial conclusions difficult.

References

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