Noradrenergic Modulation of Glymphatic Influx in Nonhuman Primates With Contrast MRI

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BACKGROUND

- The glymphatic system is a brain-wide network that facilitates cerebrospinal fluid (CSF) – interstitial fluid (ISF) solute clearance[1]
- ***Role of norepinephrine (NE) in the regulation of glymphatic function***
  - Glymphatic activity is higher during sleep[2], when NE tone is reduced
  - In rodents, pharmacological blockade of NE signaling enhances glymphatic transport[2]
  - NE-mediated vasomotion is a key driver of glymphatic function[3]
- ***Prazosin to modulate central NE and improve glymphatic clearance***
  - Alpha-1 adrenergic receptor blocker
  - Crosses the blood brain barrier with central effects
    - *Peripheral effects of lowered blood pressure may need to be managed*
  - FDA approved oral medication

HYPOTHESIS *Prazosin will increase glymphatic influx of cisterna magna administered gadolinium contrast in NHPs, measured with Dynamic Contrast Enhanced MRI*

EXPERIMENTAL DESIGN

- 6 healthy adult rhesus macaques (3 male/3 female; 8–15 years)
- 2 dynamic contrast-enhanced (DCE) MRI sessions separated by ≥1 month
- Siemens 3T Prisma Fit (Syngo MR E11) at the Oregon National Primate Research Center
- Sedated with ketamine HCl (5–15 mg/kg IM); inhaled 1.5 % isoflurane

MRI Session: total time = 4.5 hours

Contrast Injection
- Animal removed from bore w/o table or coil repositioning
- **Cisterna magna injection gadoteridol**: 0.1ml of 0.5M; 558.7 g/mol

Pre-Contrast MRI: 30 mins

Structural: T1W MPRAGE and T2W SPACE 0.8 mm³	Quantitative T1 mapping at 0.8 mm³

10 mins

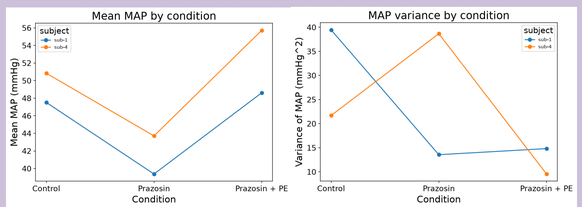
Post-Contrast DCE MRI: ~4 hours

3D T1W CAIPIRINHA VIBE: Coronal; TR/TE = 15/1.9 ms; matrix = 160x160x144; resolution = 0.8 mm³; acceleration factor = 4; slice oversampling = 22%; Partial Fourier = 7/8; Pre-contrast flip angle = 3°, 6°, 9°, 12°, and 15°; Post-contrast flip angle = 9°; **time per image = 3 mins**

EXPERIMENTAL CONDITIONS

1. ***Control:***
   - isoflurane anesthesia
2. ***Prazosin:***
   - 5 mg/kg max dose = 0.375 mg/kg/hr loading for 0.75 hr; 0.0525 mg/kg/hr maintenance for 4 hr; 1 mg/mL PZN in 5% Dextrose + isoflurane anesthesia
3. ***Prazosin + phenylephrine:***
   - to stabilize BP: 0-1.5 µg/kg/min + isoflurane anesthesia

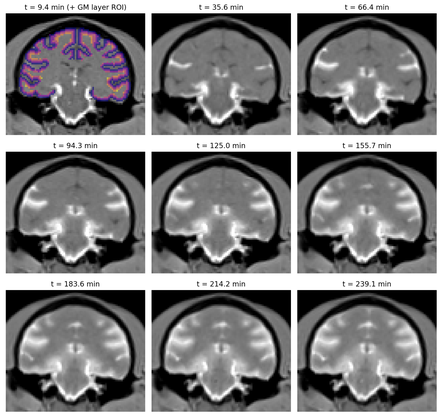
Mean Arterial Blood Pressure Across Conditions



MAP Mean and Variance for each condition. Data are currently available for only two subjects. Prazosin caused a mean decrease in MAP that was stabilized with PE.

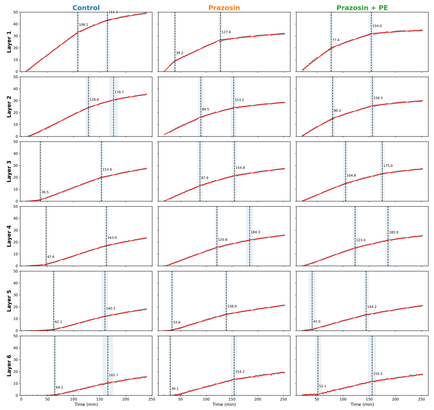
CONTRAST ENHANCEMENT FOLLOWING CM INJECTION

Progressive Signal Change on DCE MRI



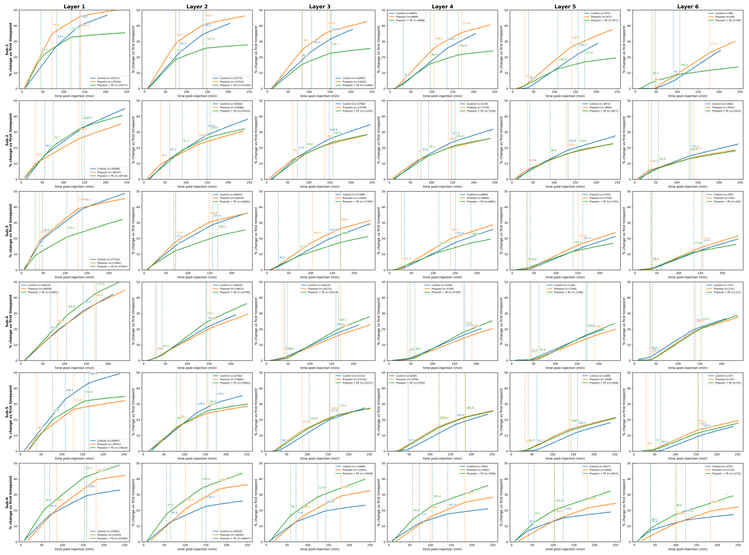
Coronal DCE-MRI of a representative animal in the control condition. A custom cortical GM mask was created to avoid any enhancing regions on the initial post-contrast timepoint and partitioned into descending layers from the cortical surface. Selected timepoints show progressive contrast enhancement over the ~4-hour period after contrast delivery. Shared intensity scale (a.u.)

Piecewise-Linear Regression



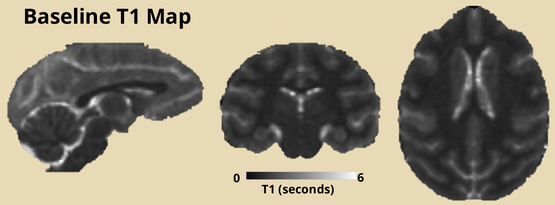
Piecewise regression[5] fits of gray matter contrast enhancement across cortical depth and pharmacological condition. Rows: GM depth layers 1 (pial surface) through 6 (deep cortex, near the gray/white boundary); columns: three conditions (Control, Prazosin, Prazosin + PE). Each panel plots percent signal change relative to the first timepoint (gray points) against time since contrast injection, with the best-fit two-breakpoint piecewise regression (red line), estimated breakpoint locations (black dashed vertical lines) and their 95% confidence intervals (blue shading), and the corresponding breakpoint times (min) labeled.

Breakpoints Across All Subjects and Conditions



QUANTITATIVE T1 MAP OF THE RHESUS MACAQUE BRAIN

Baseline T1 Map



Baseline T1 Values

Tissue	T1 (ms)
CSF	1.8 ± 0.16
Cortical Gray Matter	1.43 ± 0.04
Subcortical Gray Matter	1.34 ± 0.04
White Matter	1.1 ± 0.05

T1 fitting was done using a variable flip angle method. Images acquired at FA = 3, 6, 9, 12, and 15 degrees were motion corrected, and T1 maps were calculated using a nonlinear fit (South Edinburgh Perfusion+ Analysis Library (SEPAL) in Python). DCE images were motion corrected and registered to subject-specific MPRAGE, which were subsequently transformed to the NIMH Macaque Template (NMT v2.044) using ANTsPy (v0.5.4). ROIs for the baseline values are from the NMT segmentation atlas.

INITIAL INSIGHTS AND FUTURE DIRECTIONS

- Glymphatic influx can be quantified in a *highly translational NHP model*
- Initial observations suggest acute prazosin may not be beneficial to glymphatic influx but with notable inter-animal variability
- Possibly confounded by isoflurane anesthesia. Future work will use alternative anesthetic agents or avoid anesthetized measurements altogether
- Explore machine learning strategies to understand influx patterns on a voxel-wise basis
- Evaluate glymphatic function across the lifespan of the rhesus macaque with the aging colony at ONPRC

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