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CAI^2R Center for Advanced Imaging Innovation and Research

CSF Bulk Flow in the Human Brain via Dynamic Sodium (^{23}Na) MRI

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July 23, 2022

Declaration of Financial Interests or Relationships

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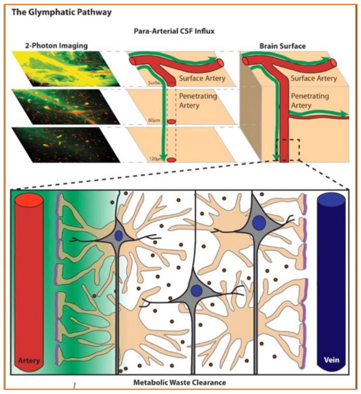
I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

The Problem – CSF Clearance

- Cerebrospinal fluid (CSF) clears the brain [1]
- CSF clearance pathway (glymphatic system)[2]
- Disruption of CSF clearance might contribute to development of Alzheimer's disease (AD)
- AD is characterized by excessive deposition of toxic waste proteins of amyloid beta (Aβ) in the brain.



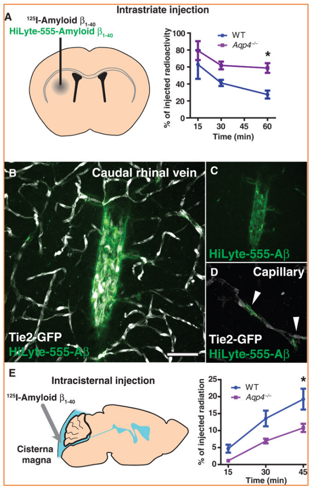
[2] Nedergaard M. *Science* ***340***, 1529–1530 (2013)

[1] Iliff JJ. Wikipedia.org. February 16, 2017

The Problem – CSF Clearance in Animals

- Recent studies of mice showed a ~**55% reduction** in Aβ clearance due to impairment of CSF clearance [3].

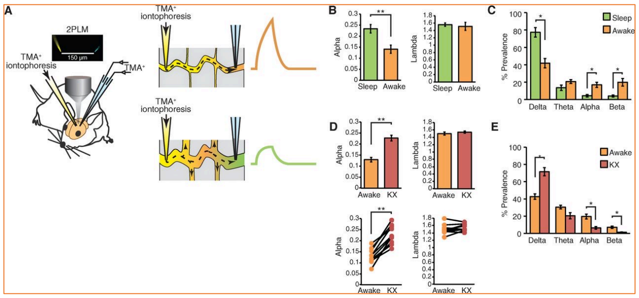
In *Aqp4*-null mice, ^{125}I-amyloid β_{1-40} clearance from the brain interstitial space was reduced by ~55%, compared to those of wild-type animals.

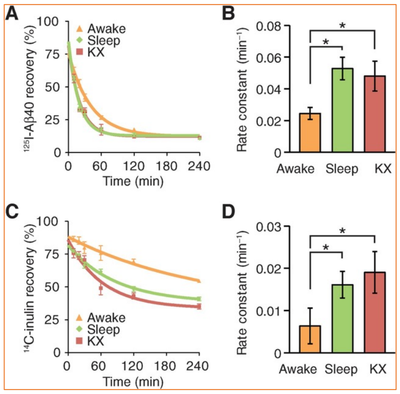


[3] Iliff JJ, et al. Sci. Transl. Med. **4** **(**147): 47ra111 (2012)

The Problem – CSF Clearance in Animals

- Sleep **increased** Aβ clearance in mice by **100%** due to enhancement of CSF flow caused by >**60% increase** in extracellular space [4].





KX: anesthetized with ketamine/xylazine

[4] Xie L, et al. Science. 2013 October 18; 342(6156).

The Problem – CSF Clearance in Humans

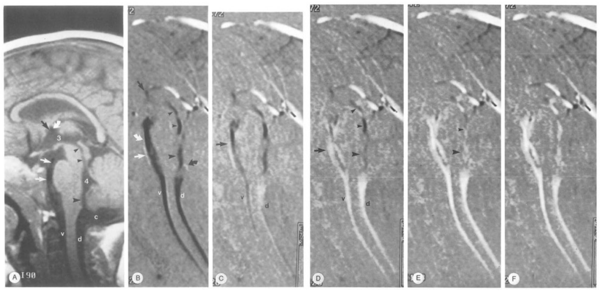
- It's **unclear** whether the impairment and enhancement exist in humans.
- Technical limitations on non-invasive approaches **hinder** adequate study.

The Significance – CSF Bulk Flow in Humans

- Yield the knowledge for CSF clearance degeneration **with normal aging** and disruption **in AD patients.**
- Determine whether CSF clearance is enhanced during sleep.
- Help develop and determine effective interventions to AD and benefit millions of people with the disease.
- CSF-related main processes: production (at choroid plexus), **bulk flow** (in parenchyma), and drainage (at arachnoid villi) of CSF, in addition to perivascular space.

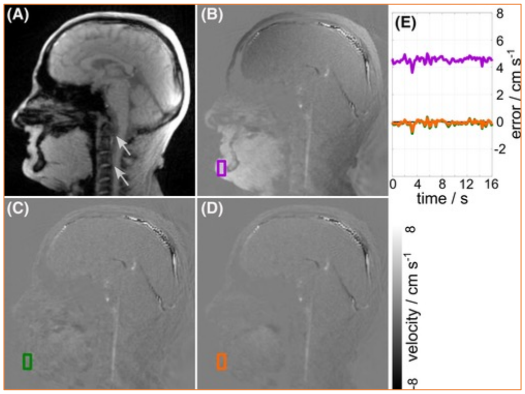
Current Techniques – Proton (1H) MRI

Phase-contrast (PC) MRI measures CSF flow just at the aqueduct and ventricles, instead of brain tissues[1,2].



[1] Naidich TP, et al. **Neurosurg Clin N Am** 1993 Oct 1;4(4):677-705.

T1w-image and a series of phase-contrast images for CSF flow from a healthy 5-year-old boy.

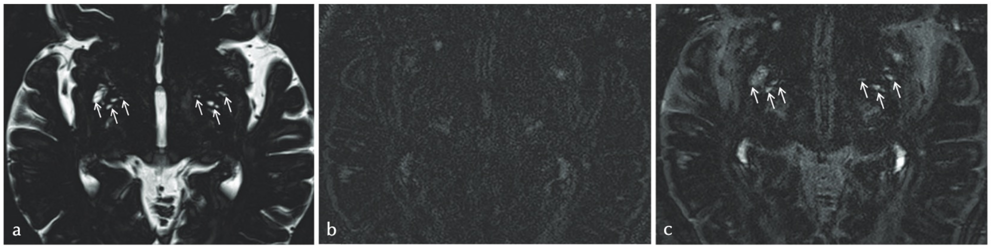


[2] Kollmeier JM, et al. **Magn Reson Med**. 2021; 87 (4): 1863-1875.

Phase-contrast image and velocity mapping for CSF flow from a healthy adult.

Current Techniques – Proton (1H) MRI

Contrast-enhanced (CE) MRI only tracks CSF flow in perivascular space[1,2].



[1] Naganawa et al. Magn Reson Med Sci 2017. 16(1):61-65. [2] Ahn SJ, et al. J Magn Reson Imaging. 2022 Feb 15.

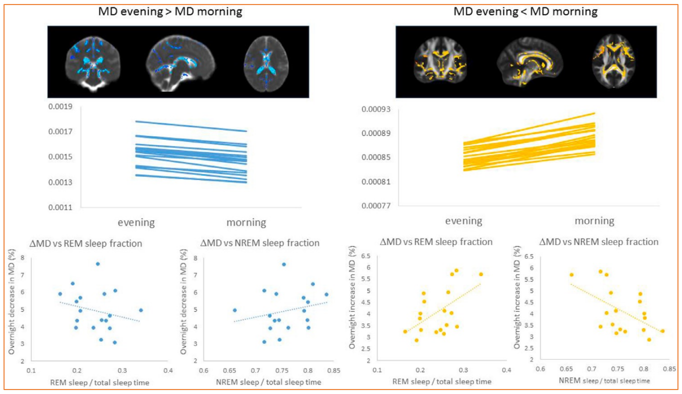
A 71-year-old woman. **(a)** Perivascular space (PVS) in the bilateral basal ganglia (arrows). **(b)** Pre-contrast heavily-T2-weighted FLAIR (hT2-FL), the PVS has a low-signal intensity. **(c)** Post-contrast hT2-FL (4hr post), PVS increased signal intensity (arrows). The CSF also has increased signal. **Intravenous Gadolinium-based contrast agent (IV-GBCA)**.

Current Techniques – Proton (1H) MRI

Low-b value diffusion tensor imaging (DTI) may assess local flow at the entry of CSF drainage [1].

b = 1000 s/mm^2, 35 directions, TE/TR= 77/ 6000ms

Mean diffusivity (MD) Evening vs. morning: **Decreased** in the CSF spaces (left panel), **Increased** in brain regions (right panel), including the periventricular white matter, basal ganglia, thalamus, cingulate gyrus, cerebellum and brainstem.

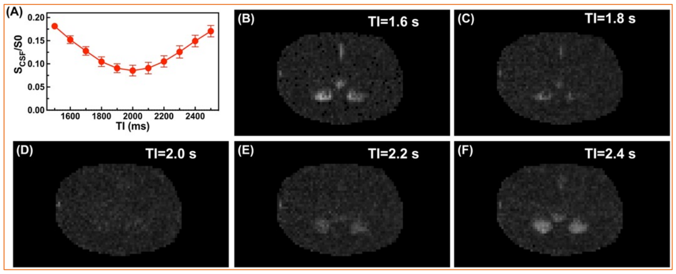


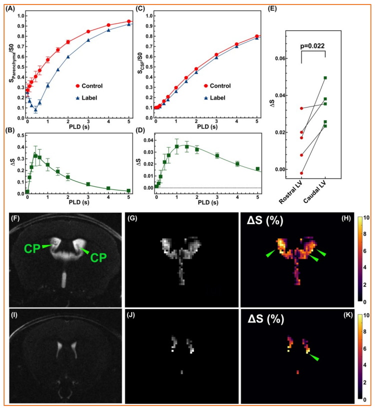
[1] Tuura RO, et al. ISMRM 2019. p.752; or NeuroImage 241 (2021) 118420 .

Current Techniques – Proton (1H) MRI

Phase alternate labeling with null recovery (PALAN) that labels the other components by flipping the phase of pulses when CSF is nulled[1].

The cerebrospinal fluid (CSF) signal as a function of TI for the third and lateral ventricles. The typical whole brain images for different TI values: 1.6 (B), 1.8 (C), 2.0 (D), 2.2 (E), and 2.4 s (F)



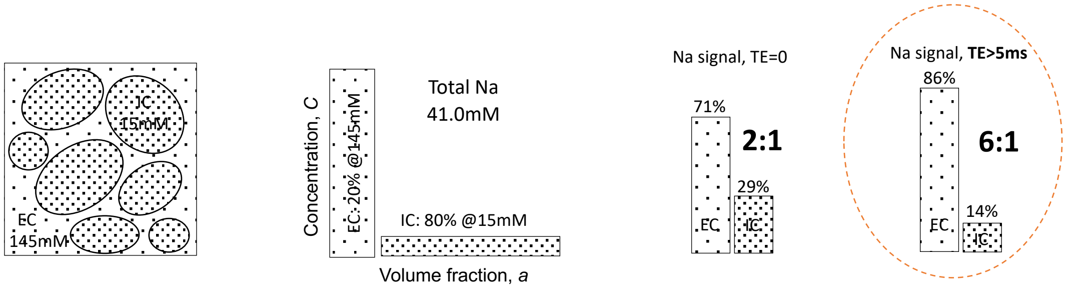


[1] Li AM, et al. Magn Reson Med. 2022 Mar;87(3):1207-17.

Current Techniques – Proton (1H) MRI

- **No known** proton (^{1}H) MRI approaches are capable of distinguishing CSF from water in the brain parenchyma without tracer injection.
- Here we **propose** dynamic sodium (^{23}Na) MRI to map CSF flow in the human brain parenchyma **without the need for external tracers**.

Why Na MRI? – Tissue basis



A. Voxel model B. The a-*C* graph C. Relative Na signal at TE=0 or >5 ms

Schematic of tissue basis for sodium MRI in the brain[1]: **a**) sodium in intra-/extra-cellular compartments at a voxel, **b**) the *a-C* graph for volume fraction *a* and sodium concentration *C*, and **c**) relative sodium signal intensity at a voxel at echo time TE=0 or >5 ms. **The long TE (>5ms) leads to a 60% reduction of intracellular Na signal, and thus further increases the contrast between extra- and intra-cellular spaces.**

[1] Thurborn KR. NeuroImaging 2018. 168:250-268.

Why Na MRI? – Na signal vs. extracellular volume

In a normal case:

$s = \Delta V\,(a_e C_e + a_i C_i) = \Delta V\,(145 a_e + 15 a_i)$, at TE=0ms

$s = \Delta V\,(145 a_e + 0.4 * 15 a_i)$, at TE>5ms

In a change of extracellular volume:

$\delta s = \Delta V\,[\delta a_e (C_e - C_i) + C_i] = \Delta V\,(130\,\delta a_e + 15)$, at TE=0ms

$\delta s = \Delta V\,(139\,\delta a_e + 6)$, at TE>5ms

A change in extracellular space can be amplified in Na signal by ~140x times!

Dynamic Sodium (^{23}Na) MRI – Challenges

- ➢ Need a series of 3D sodium images of whole brain at a high temporal resolution to snapshot CSF movement.
- ➢ Ideally, need a full k-space data for each time frame.
- ➢ Need frame acquisition time shorter than CSF movement (~150mm/s at the aqueduct).
- ➢ An extremely low SNR (~5–50) and short T2 relaxation time ($T2_{long}$ ~ 30ms).
- ➢ A typical 3D sodium MRI at 3T needs 2.7min for a frame, too long to be dynamic imaging.

Dynamic Na MRI – Data Acquisition Strategies

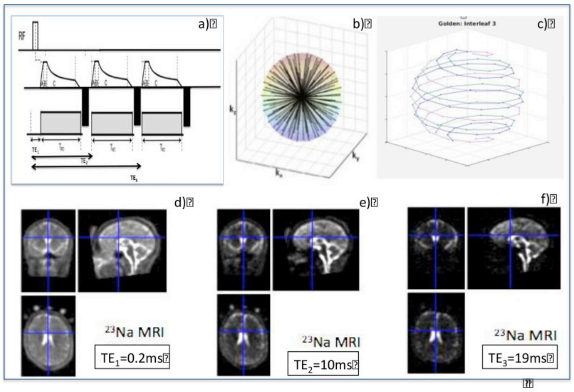
Adopt from dynamic proton (1H) MRI?

- o The “**keyhole**” approach, tried by Bydder et al [1] using golden-angle radial acquisitions and achieving a temporal resolution of 28.8sec.
- o The “**view sharing**” approach, neighboring frames share part of k-space lines.
- o The “**k-t sparse**” approach, using spatial and temporal sparsity of frame images and under-sampling the k-space at each frame.
- o The “**GRASP**” approach, under-sampling the k-space along radial lines at golden angles, and then using compressed sensing (CS) algorithms for recon.
- o The “**low-rank + sparsity**” approach, individual frame images considered a nearly-static (or low-rank) image plus a highly-sparse dynamic image.

Unfortunately, the k-t sparse, GRASP, and L+S were concepted upon high SNR and may not directly applicable to dynamic sodium MRI.

[1] Bydder et al. NeuroImage. 2019; 184:771-780.

Dynamic Na MRI – Data Acquisition Strategies

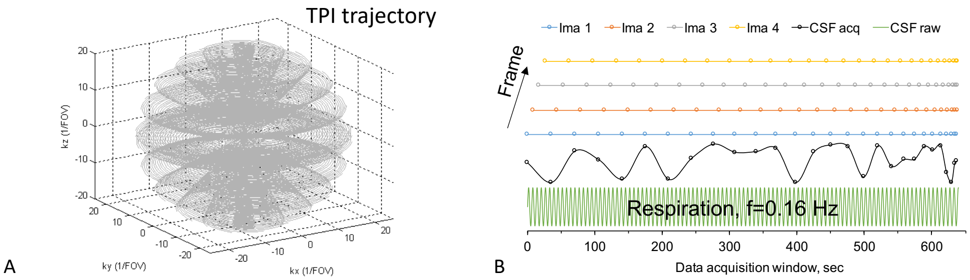


[1] Bydder et al. NeuroImage. 2019; 184:771-780.

Dynamic Na MRI: a full k-space sampling and then a partial k-space updates with 3D golden angles.

A low temporal resolution of 29 s.

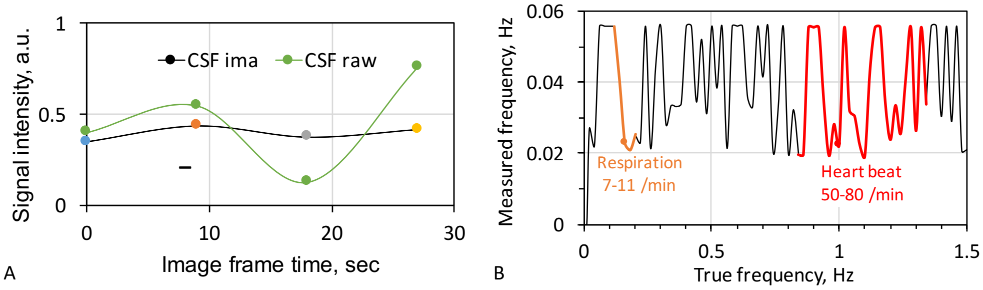
Dynamic Na MRI – Sliding Time Window



[1] Qian Y, et al. ISMRM 2020. p189. [2] Boada FE, et al. MRM 1997. 37:706-716.

Data acquisition (interleaved viewing)[1] : a) The 3D k-space sampling of the TPI trajectory[2] for each frame, and **b**) the interleaved viewing (dots) for 4 frames, with the measured (black) and true (green) Na signals varying with respiration. The loop order is **{**ring 1:nr **{**frame 1:nf **{**projections 1:np**} } }**.

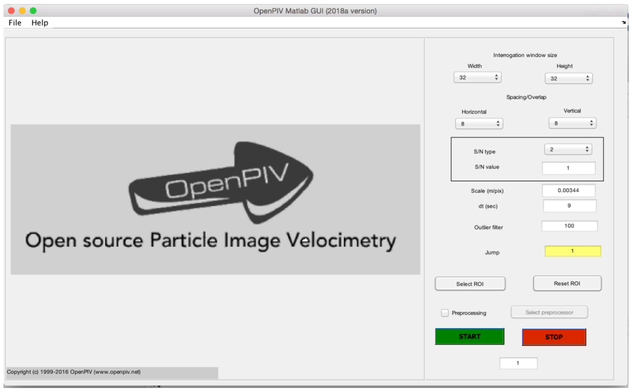
Dynamic Na MRI – Computer simulations



[1] Qian Y, et al. ISMRM 2020. p189.

a) Computer simulated CSF signal changing with time frame (ima) from the dynamic Na MRI against the true (raw) value at respiration frequency 0.16 Hz, and **b**) the frequency measured at the frames against true frequency. These show that the change of CSF signal at respiration and heart beat frequencies is detectable by the dynamic Na MRI with a total scan time of 10.64 min for 4 frames.

CSF Velocity Mapping – OpenPIV



Interrogation window size
Width: 32
Height: 32
Spacing/Overlap
Horizontal: 8
Vertical: 8
S/N type: 2
S/N value: 1
Scale (m/pix): 0.00344
dt (sec): 9
Outlier filter: 100
Jump: 1

Interface of OpenPIV [1].

Velocity map (vector field) of CSF bulk flow was calculated on the time frame images using an open-source software **OpenPIV** (Matlab verion 2.5)[1].

We used an interrogation window 32x32 pixels and a spacing step 8x8 pixels.

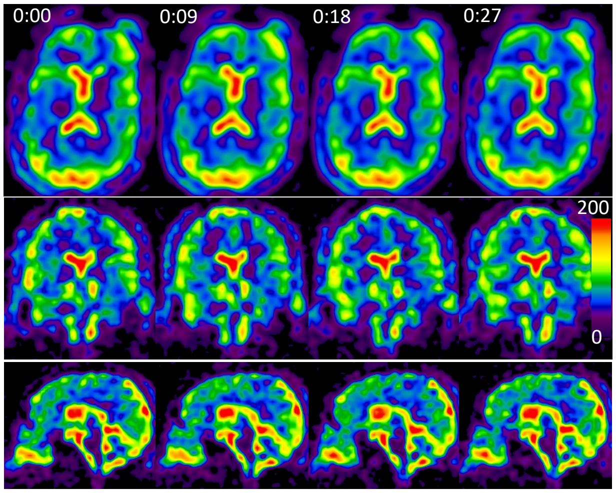
[1] Taylor et al. IEEE Trans Instrum Meas 2010. 59(12):3262-3269.

Dynamic Na MRI – Human subject study

- Approved by our institutional IRB at NYU Langone Health.
- Cognitively Normal (CN) subjects (n=4, male/female, age 24-72 years).
- Sodium MRI: 3T Scanner (Siemens Prisma), custom-built 8-channel dual-tuned (^{1}H-^{23}Na) head array coil[1], custom-developed TPI sequence[2,] FOV=220 mm, matrix size=64, 3D isotropic, TE/TR=5/100ms, flip angle=90º, averages=1, frames=4, and TA=10:28.
- Sodium image recon: offline with a program customer-developed in C++.

[1] Lakshmanan et al. NMR Biomed 2018. 31:e3867. [2] Boada et al. MRM 1997. 37:706-716.

Dynamic Na MRI – Sodium Image Frames



Time frames of dynamic 3D sodium MRI on a young male subjects at age of 27 years.

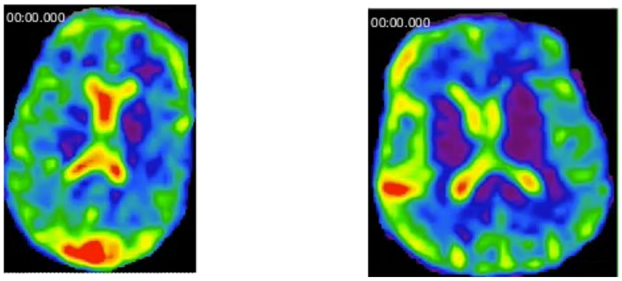
Color scale is the relative image intensity. There was no correction for the modulation of coil sensitivity.

[1] Qian Y, et al. ISMRM 2020. p189.

Dynamic Na MRI – Examples (Young vs. Older)

A. 27-year-old

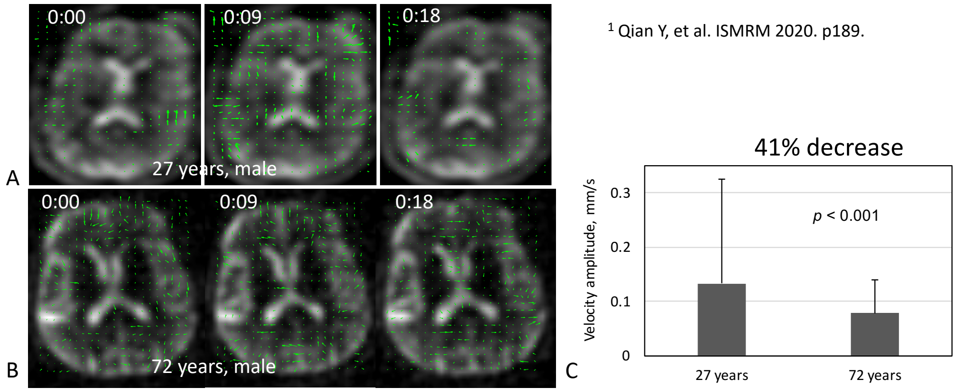
B. 72-year-old



[1] Qian Y, et al. ISMRM 2020. p189.

Videos of the dynamic sodium MRI images (linear interpolation in time for display purpose only) show a continuous flow of CSF into and out of the tissues in the brain for clearance: **a**) the 27-year-old male subject, and **b**) the 72-year-old male subject.

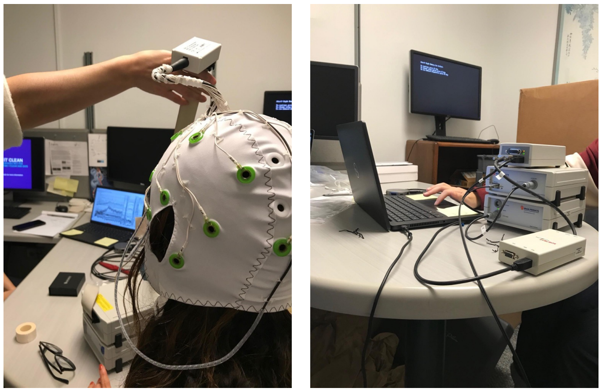
Applications – CSF velocity (Young vs. Older)



[1] Qian Y, et al. ISMRM 2020. p189.

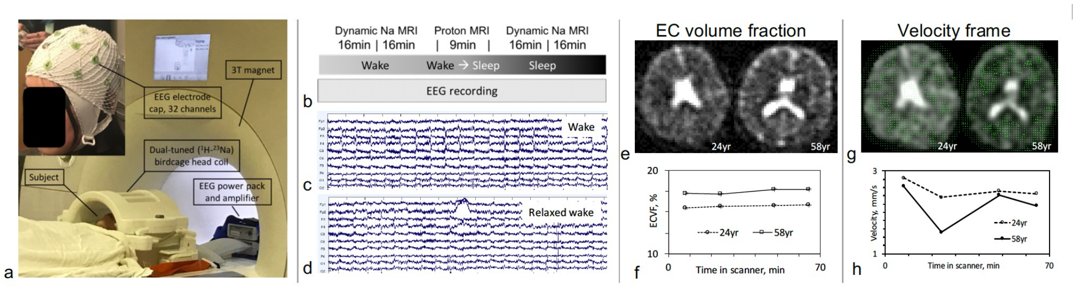
Time frames of CSF velocity (blue arrows) maps from dynamic 3D sodium MRI on two male subjects: **a**) the young brain, **b**) the older brain, and **c**) the largest mean magnitude of in-plane velocity.

Dynamic Na MRI – MRI+EEG Sleep Impact Study



Testing the EEG system (Brain Vision) outside MRI scanner room: Set-up and recordings.

Dynamic Na MRI with EEG – Preliminary Results



[redacted]

Dynamic Na MRI with EEG for sleep impact study at 3T. **a)** The MRI-EEG systems. **b)** Timing for the MRI, EEG, and wake-sleep. **c,d)** EEG signals (15-sec long, including F4, C4, and O2 for sleep staging) of a healthy subject (58yr, female), right before the 1st and 4th Na MRI scans. **e)** Extra-cellular volume fraction (ECVF) map at the 1st Na scan. **f)** Slice-based ROI mean of ECVF over gray matter against time. **g)** CSF velocity map at the 1st frame of the 1st Na MRI scan. **h)** Slice-based mean velocity magnitude of CSF flow against time.

Discussion

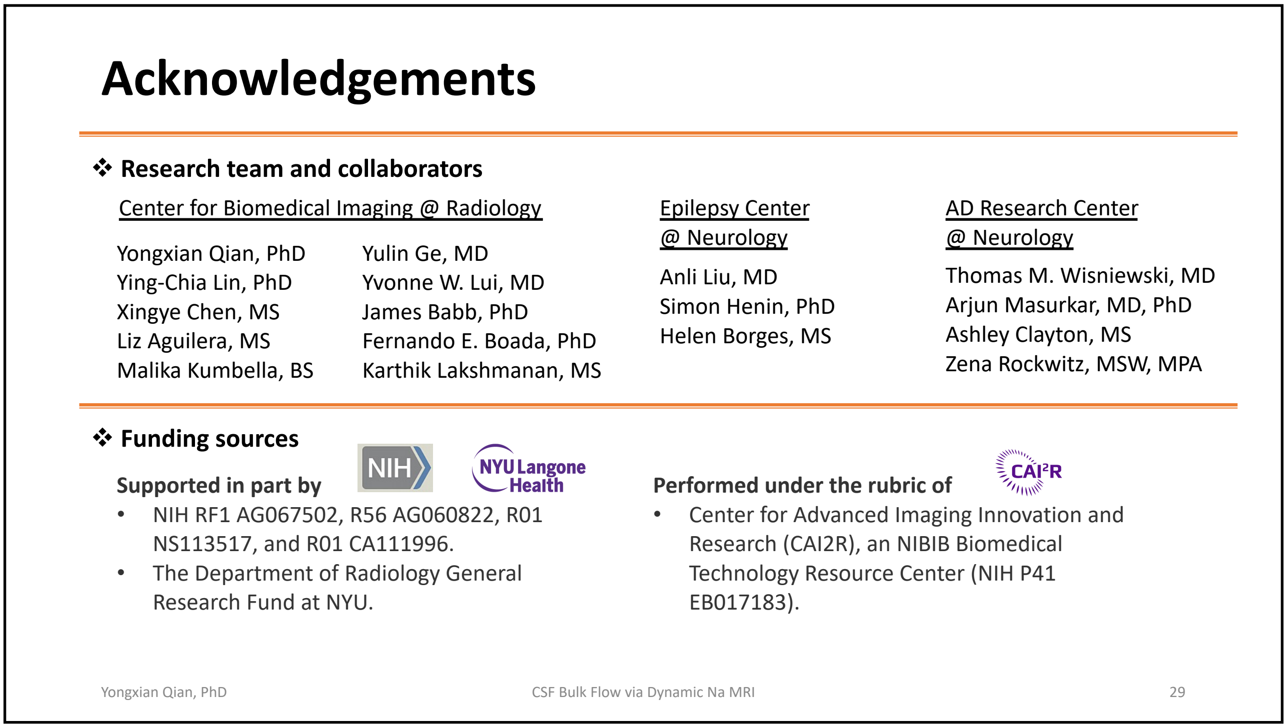
- ✓ The dynamic Na MRI was shown to be **able to map** the velocity of CSF bulk flow in the brain parenchyma.
- ✓ Mean magnitude of CSF bulk flow velocity was **decreased** by 41% from young (27yr) to older (72yr) brains, **an encouraging finding!**
- ✓ **However,** more subject studies are needed **to confirm** this finding.
- ✓ The velocity was calculated in-plane (V_x, V_y), and needs **to be extended to 3D** (V_x, V_y, V_z) to view a full picture of CSF bulk flow.
- ✓ The temporal resolution (9 s) needs **to be further improved** to catch a full-range effect of respiration and heart beat on CSF bulk flow.

Summary

- ❑ For the first time, dynamic sodium MRI was demonstrated **to be feasible** to map velocity of CSF bulk flow without the need for external tracers.
- ❑ More efforts are needed to **improve the temporal resolution** of dynamic sodium MRI **and the velocity measurement accuracy** of CSF bulk flow in the brain.

It is worth to mention:

- ❑ Sodium MRI is not able to distinguish between CSF and blood or interstitial fluid in the brain parenchyma as they have the same sodium concentration and co-exist in extracellular space.



Acknowledgements

❖ **Research team and collaborators**

Center for Biomedical Imaging @ Radiology

Yongxian Qian, PhD
Ying-Chia Lin, PhD
Xingye Chen, MS
Liz Aguilera, MS
Malika Kumbella, BS

Yulin Ge, MD
Yvonne W. Lui, MD
James Babb, PhD
Fernando E. Boada, PhD
Karthik Lakshmanan, MS

Epilepsy Center @ Neurology

Anli Liu, MD
Simon Henin, PhD
Helen Borges, MS

AD Research Center @ Neurology

Thomas M. Wisniewski, MD
Arjun Masurkar, MD, PhD
Ashley Clayton, MS
Zena Rockwitz, MSW, MPA

❖ **Funding sources**

Supported in part by

- NIH RF1 AG067502, R56 AG060822, R01 NS113517, and R01 CA111996.
- The Department of Radiology General Research Fund at NYU.

Performed under the rubric of

- Center for Advanced Imaging Innovation and Research (CAI2R), an NIBIB Biomedical Technology Resource Center (NIH P41 EB017183).