Characterizing CSF volume change across functional activation, alertness states, and breath-hold tasks at 7T

Stephanie Swegle[1], Renzo Huber[1,2], Javier Gonzalez-Castillo[1], Burak Akin[1], Rüdiger Stirnberg[3], A. Tyler Morgan[1], Peter Molfese[1], Daniel Handwerker[1], Catherine Walsh[1], Chung (Kenny) Kan[1], Peter A. Bandettini[1]

[1]NIH, Bethesda, MD, United States, 20892
[2]Athinoula A. Martinos Center for Biomedical Imaging, Mass General Brigham, Radiology Harvard medical school, Charlestown, MA, USA
[3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

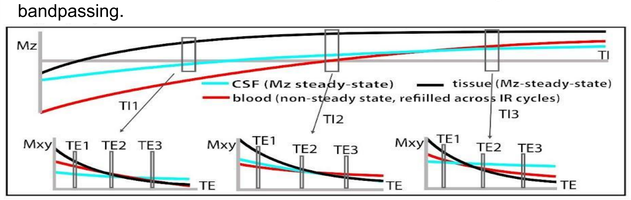
Poster #124

INTRODUCTION

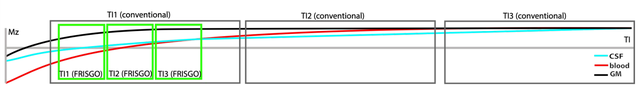
- Dynamic cerebrospinal fluid (CSF) acts as a clearance system in the human brain, removing waste and toxins, especially during sleep[1-3] .
- Most functional CSF tracking with fMRI has focused on CSF flow[1-5], where sensitivity and efficiency is difficult; CSF volume may be more straightforwardly measured.
- CSF volume changes can be a contributor and contaminant in Vascular Space Occupancy (VASO)[9-13].
- We use a VASO-like inversion recovery (IR) sequence to capture CSF volume changes. Specifically, we propose an inversion recovery 7T 3D-EPI protocol that uses CSF's specific relaxation "fingerprint" to capture voxel-specific CSF volume fractions independent of dynamic changes in cerebral blood volume (CBV) and BOLD.
- We use breath hold tasks, visual activation tasks and eye tracking to validate our sequence and test how CSF dynamics are modulated by different states of alertness and tasks.
- We expect that our sequence will show anticorrelation between CSF and CBV in the visual cortex during flickering checkerboard task. This visual task should cause blood to come into the visual cortex, causing CSF to leave the area due to the Monro-Kellie doctrine[6].
- Breath holding is known to cause blood volume to increase globally, and so due to the Monro-Kellie doctrine[6], we would expect CSF volume to decrease globally. When blood volume increases and veins expand, we would expect CSF to be pushed out of the area due to the increasing space taken up by veins.
- We are using these tasks and expectations to validate our sequence's ability to capture changes in CSF volume without CBV and BOLD contamination, and to further elucidate CSF dynamics.

METHODS

- We use a multi-echo, multi-TI, 3DEPI approach, combining three echo times and three inversion times.
- Our sequence groups 27 shots into 9 echo planar k-space sets/volumes.
- We collect data at 7T (Siemens, Germany), using a 8Tx/32Rx head coil (Nova, USA)) and 3D-EPI with Skipped-CAIPI[14]. FRISGO[8] is used to capture images in time scales of T1.
- Scan parameters: TR=3.2s, TE1/TE2/TE3=8.24/30.34/52.44ms, TI1/TI2/TI3=712.5/1601.5/2490.5ms, flip angle=45, varflip=0. FOV 220mm, with a voxel size of 2.6mm iso & #of Volumes:185
- Assumed T1 values (Bloch modeling): GM/blood/CSF = 1950/2100/4000ms, T2* GM/blood/CSF/WM = 33.2/37.5/4000ms/26.8[15-18].
- We have scanned 4 healthy volunteers with these parameters.
- Visual task: 10 minute block design (30sec blocks) with flashing checkerboards, bilateral and unilateral runs.
- Breath hold task: 15sec of breath hold task each proceeded by inhale or exhale followed by 30 sec of free breathing for 10 repetitions totaling to 10 minutes.
- Rest: 10 minute resting state collected, with fixation cross.
- Physiological recording to track changes in respiration[19] (BIOPAC) and in-scanner eye tracking (EyeLink-1000Plus, SR-Research) were done simultaneously to fMRI.
- Image processing: AFNI, FSL and MATLAB.
- To process the data, we run separate ICAs using melodic on each of the nine inversion time and echo time combinations. Then, we manually remove ICA components that are noisy.
- Processing of the data included motion correction, detrending and bandpassing.



Each inversion time/echo time combination is expected to have a unique fingerprint of tissue type specific signals. Our sequence nulls CSF at inversion time 1 and nulls CBV at inversion time 2.



Segmentation across IR cycles + advanced readout acceleration (FRISGO) is needed to capture dynamics of inversion recovery.

RESULTS

Overview of the data:

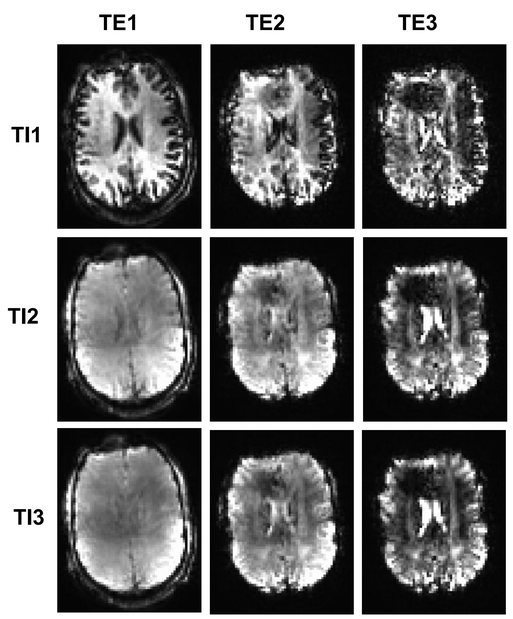


Figure 1: This figure shows our multi-echo multi-inversion data. The darker the area is, the more nulled it is. The combination of inversion time one and echo time one is where we expect to be most sensitive to CSF volume because that is where CSF is nulled. We expect to be most sensitive to CBV in the second inversion time and first echo because that is where CBV is nulled. We expect to be most sensitive to BOLD in the second echo because it matches most closely to the echo time normally used for BOLD. We collect a third inversion time for comparison.

Visual task:

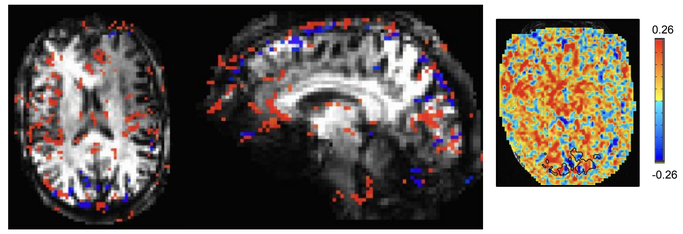


Figure 2: This figure shows a map of the CSF weighted image correlated to the CBV weighted image from the bilateral visual checkerboard task. The two images on the left have a threshold of 0.3 and a minimum cluster size of 5 voxels. The image on the right is not thresholded and includes black lines showing where the BOLD response was located during the visual task, showing areas where the checkerboard task should be affecting. Red indicates areas where CSF and CBV are correlated and blue indicates areas where CSF and CBV are anticorrelated.

Breath hold task:

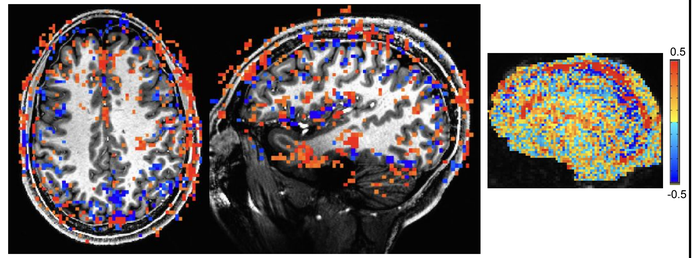


Figure 3: This figure shows a correlation map of the CSF weighted image correlated to the CBV weighted image for the data collected during the inhold breath holding task. The two images on the left have a threshold of 0.3 and a minimum cluster size of 5 voxels. The image on the right is not thresholded. Red indicates areas where CSF and CBV are correlated and blue indicates areas where CSF and CBV are anticorrelated.

Task timecourses:

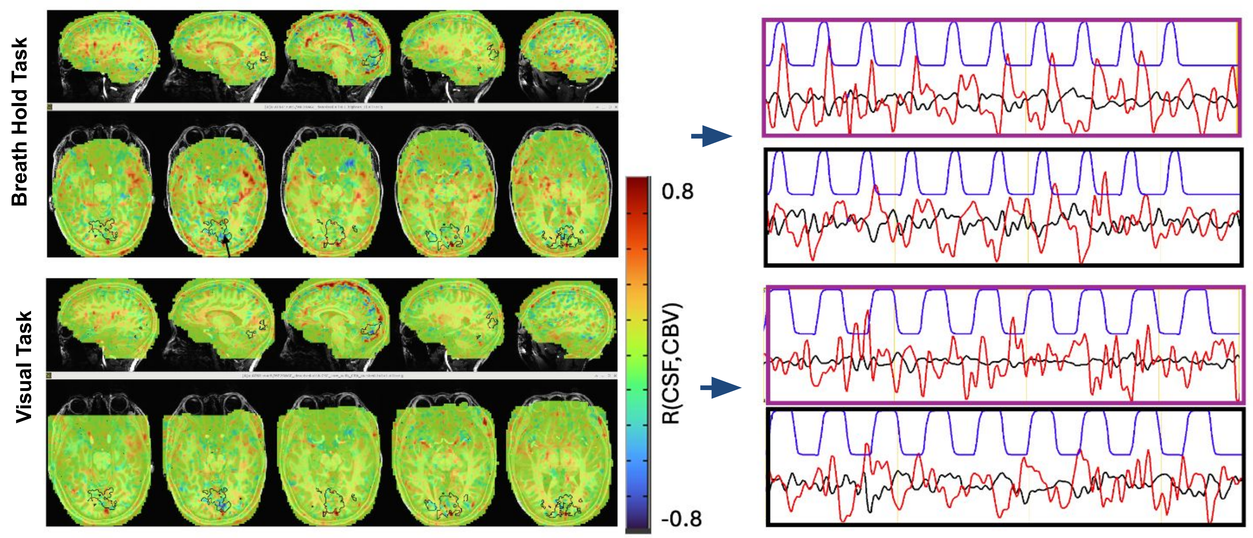


Figure 4: This figure shows the breath hold (inhold) task data on the top two panels, and the bilateral visual checkerboard task on the bottom two panels. This is the same map of correlation between CSF and CBV weighted data as in Figure 2 and Figure 3, except that it has been spatially upsampled to highlight some potential underlying structure. The arrows on the images point to where the timecourses on the right are coming from. The black lines on the images indicate where the BOLD response is located for the visual checkerboard task, highlighting areas we would expect the task to activate. On the timecoures, the task paradigm is shown in blue (ideal response), the CBV timecourse is shown in red and the CSF timecourse is shown in black.

CONCLUSIONS

- We are seeing preliminary examples of CSF and CBV anticorrelated where we would expect.
- It appears as though our sequence is effectively able to separate CSF and CBV due to CSF and CBV being anticorrelated in the visual cortex for the flickering checkerboard task.
- With the visual task, the CSF/CBV anticorrelation follows where we would expect it to be based on BOLD activation during the task
- In the breath hold task, it appears as though there is a global response and global anticorrelation patterns between CSF and CBV. In the visual checkerboard task, we see a more localized response, which follows with previous findings of localized CSF flow in response to visual stimulus[20].
- From the visual task to the breath hold task, we see an increased global effect. This makes sense given that the breath hold task should trigger more of a vascular response throughout the whole brain. CSF and CBV are especially inversely correlated around the sagittal sinus, insula and potentially perivascular spaces. This could be due to venous expansion pushing CSF out of the areas as a part of the glymphatic system.

FUTURE DIRECTIONS

- Future work will include analysis of eye tracking data and physiological data to see how drowsiness and physiological changes impact CSF volume change.
- We have collected data where participants have gotten drowsy and fallen asleep, so we plan to use this data to examine how drowsiness and sleep impact global CSF volume change.
- Future work also includes looking into how BOLD and CSF volume are related to each other and how to better disentangle BOLD from the CSF weighted data.
- We also hope to look further into creating synthetic images that further separate CSF, BOLD and CBV.

REFERENCES

1) Fultz, Nina E et al. "Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep." Science (New York, N.Y.) vol. 366,6465 (2019): 628-631. doi:10.1126/science.aax5440
2) Kim, J.-H., Im, J.-G., & Park, S.-H. "Measurement of CSF pulsation from EPI-based human fMRI." Neuroimage 257 (2022): 119293. https://doi.org/10.1016/j.neuroimage.2022.119293
3) Grubb, S., Lauritzen, M., 2019. Deep sleep drives brain fluid oscillations. Sci New York N Y 366, 572–573. doi:10.1126/science.aaz5191.
4) Wang, F., Reese, T., Rosen, B., Wald, L., Lewis, L., Polimeni, J., Dong, Z., "Simultaneous 4D CSF flowmetry and BOLD fMRI using EPTI for investigation of neural activity evoked CSF flow responses." 2024. ISMRM Annual Meeting and Exhibition, Singapore.
5) Gonzalez-Castillo, J., Fernandez, I.S., Handwerker, D.A., Bandettini, P.A., 2022. Ultra-slow fMRI fluctuations in the fourth ventricle as a marker of drowsiness. NeuroImage 259, 119424. https://doi.org/10.1016/j.neuroimage.2022.119424
6) Mokri, B., 2001. The Monro-Kellie hypothesis: Applications in CSF volume depletion. Neurology 56, 1746–1748. doi:10.1212/wnl.56.12.1746
7) Lu, H., Hua, J., van Zijl, P.C.M., 2013. Noninvasive functional imaging of cerebral blood volume with vascular-space-occupancy (VASO) MRI. NMR in Biomedicine 26, 932–948. https://doi.org/10.1002/nbm.2905
8) Renzo Huber[1], Michael Koehler[2], Ruediger Stirnberg[3], Jennifer Evans[1], Lasse Knudsen[4], A. Tyler Morgan[1], David Feinberg[5], Daniel Handwerker[1], Marly Rubin[1], Burak Akin[1], Stephanie Swegle[1], Peter Bandettini[1]"Advanced Echo-planar Parallel Imaging with Gradient Harmonization (AEPIG): an optimization strategy for fast high resolution fMRI." 2025.
9) Jin, T., Kim, S.G., 2010. Change of the cerebrospinal fluid volume during brain activation investigated by T1ρ-weighted fMRI. NeuroImage 51, 1378–1383. https://doi.org/10.1016/j.neuroimage.2010.03.047
10) Donahue, M.J., Lu, H., Jones, C.K., Edden, R.A.E., Pekar, J.J., Van Zijl, P.C.M., 2006. Theoretical and experimental investigation of the VASO contrast mechanism. Magnetic Resonance in Medicine 56, 1261–1273. https://doi.org/10.1002/mrm.21072
11) Piechnik, S.K., Evans, J., Bary, L.H., Wise, R.G., Jezzard, P., 2009. Functional changes in CSF volume estimated using measurement of water T2 relaxation. Magnetic Resonance in Medicine 61, 579–586. https://doi.org/10.1002/mrm.21897
12) Ciris, P.A., Qiu, M., Constable, R.T., 2014. Noninvasive MRI measurement of the absolute cerebral blood volume-cerebral blood flow relationship during visual stimulation in healthy humans. Magnetic Resonance in Medicine 72, 864–875. https://doi.org/10.1002/mrm.24984
13) Scouten, A., Constable, R.T., 2008. VASO-based calculations of CBV change: Accounting for the dynamic CSF volume. Magnetic Resonance in Medicine 59, 308–315. https://doi.org/10.1002/mrm.21427
14) Stirnberg, R., Stöcker, T., 2021. Segmented K-Space Blipped-Controlled Aliasing in Parallel Imaging (Skipped-CAIPI) for High Spatiotemporal Resolution Echo Planar Imaging. Magnetic Resonance in Medicine 85, 1540–1551. https://doi.org/10.1101/2020.06.08.140699
15) Huber, Renzo. "Mapping Human Brain Activity by Functional Magnetic Resonance Imaging of Blood Volume." 2014. Universität Leipzig. https://ul.qucosa.de/landing-page/?tx_dlf[id]=https%3A%2F%2Ful.qucosa.de%2Fapi%2Fqucosa%253A13259%2Fmets
16) Huber, Laurentius , Goendr, Jozien , Kennerley, Aneurin J., Ivanov., Dimo. Krieger, Steffen N., Lepsien, Jöran , Trampe, Robert., Turner, Robert., Möller, Harald E. "Investigation of the Neurovascular Coupling in Positive and Negative BOLD Responses in Human Brain at 7T." https://eprints.gla.ac.uk/93358/1/93358.pdf
17) Ivanov, D., Schäfer, A., Deistung, A., Streicher, M.N., Kabisch, S., Hensler, I., Roggenhofer, E., Jochimsen, T.H., Schweser, F., Reichenbach, J.R., Uludag, K., Turner, R., 2013. In vivo estimation of the transverse relaxation time dependence of blood on oxygenation at 7 tesla. In Proceedings of the 21st Annual Meeting of ISMRM, Salt Lake City, Utah, USA. p. 2472.
18) Donahue, M.J., Hoogduin, H., van Zijl, P.C., Jezzard, P., Luijten, P.R., Hendrikse, J., 2011. Blood oxygenation level-dependent (BOLD) total and extravascular signal changes and ΔBold*R2′ in human visual cortex at 1.5, 3.0 and 7.0 T. NMR Biomed. 24, 25-34. doi: 10.1002/nbm.1552
19) Aktas, G., Kollmeier, J.M., Joseph, A.A., Merboldt, K.-D., Ludwig, H.-C., Gärtner, J., Frahm, J., Dreha-Kulaczewski, S., 2019. Spinal CSF flow in response to forced thoracic and abdominal respiration. Fluids Barriers CNS 16, 10. https://doi.org/10.1186/s12987-019-0130-0
20) Williams SD, Setzer B, Fultz NE, Valdivieso Z, Tacugue N, et al. (2023) Neural activity induced by sensory stimulation can drive large-scale cerebrospinal fluid flow during wakefulness in humans. PLOS Biology 21(3): e3002035. https://doi.org/10.1371/journal.pbio.3002035

ACKNOWLEDGEMENTS

We thank Michael Reel, Brittany Pollard and Shruti Japee for their help with participant scheduling logistics. We thank César Caballero-Gaudes for helpful discussions. Thank you to everyone in the Section on Functional Imaging Methods (SFIM), The FMRI Facility (FMRIF) and the layer-FMRI working group for their help and feedback on this project. We thank Jun Hua for helpful discussions.

ETHICS

MRI data were acquired under the NIH-IRB (93-M-0170, ClinicalTrials.gov: NCT00001360). We thank Shruti Japee for guidance on the IRB protocol procedures.

FUNDING

This work is supported by the NIH Intramural Program of NIMH/NINDS (#ZICMH002884), and SFIM (#ZIAMH002783). MRI scanning was performed in the FMRIF core.

CONTACT

Please email stephanie.swegle@nih.gov with any questions.