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MR/White Paper

Non-Contrast MR Evaluation of Age-Related Decline in Glymphatic Function in the Brains of Healthy Subjects

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Introduction

The glymphatic fluid clearance is thought to be the main mechanism of how the brain's metabolic wastes are cleared. Its dysfunction is potentially associated with neurodegenerative diseases such as Alzheimer's disease. The concept of glymphatic fluid clearance in the brain was pioneered by Nedergaard[1,2], who proposed a system by which waste products are eliminated from the central nervous system via cerebrospinal fluid (CSF) and interstitial fluid exchange in the paravascular space. Additionally, the pathway of CSF or fluid outflow via the glymphatic system has not been established. The classic or direct glymphatic drainage pathway has been postulated as flow from the subarachnoid space (SAS) to the superior sagittal sinus (SSS) via arachnoid granulations, but without validation using in vivo imaging techniques.[3]

Existing studies for imaging the glymphatic drainage pathway have utilized either ionizing radiation and/or invasive contrast injection[4,5], which inhibited wide-spread investigation in humans. Limited number of studies in humans using intrathecal injection of Gadolinium contrast agents have revealed uptake and washout of the tracer at the meninges as evidence of glymphatic clearance, albeit over a 48-hour period, which is unlikely given a much higher CSF production rate.

In this study, we aimed to determine the direction and relative quantity of intrinsic CSF outflow movement as measures of glymphatic function in human subjects, without utilizing contrast or other invasive injection techniques. We employed a novel arterial spin-labeling (ASL) technique with a tag-on and tag-off 3D acquisition. Additionally, as a proof-of-concept study, we evaluated glymphatic function in younger and senior healthy adults.[6,7]

Materials and Methods

This human subject's study was approved by the institutional review board and written informed consents were obtained.

Human Subjects: 16 healthy adults (10 males and 6 females; age range 19-71 years) without known neurodegenerative or cardiovascular diseases were imaged. Participants were divided into two age groups of 19 to 59 years old (n=8) and older than 60 (n=8).

MR Protocol: All MRI examinations were performed on a 3T Canon Vantage Galan MRI scanner with a 32-ch head coil. Each subject was imaged with morphologic sequences (for anatomy) along with four-dimensional (4D) fluid spin-labeling MRI using 3D centric ky–kz single shot fast spin echo (cSSFSE) acquisition in the coronal plane, at the top of the head with an oblique sagittal tag pulse next to superior sagittal sinus (Figure 1b): TR=5400 ms, TEeff = 30 ms, ETS = 5.0 ms, 6 echoes to the center of k space, flip/refocusing angle = 90/150°, SPAIR fat suppression, matrix size =368 × 368 (736 × 736 after interpolation), FOV=25 × 25 cm, parallel imaging factor of 3, 20 slices, 1 mm thick (0.5 mm after interpolation), tag-on and tag-off acquisition time of about 1 min and 48 s. Multiple inversion times (TI) of 500, 750, 1000, 1250, 1500, 2000, and 3000 ms were used.

Analysis: First, we performed simple image subtraction between tag-on (Figure 1b) and tag-off (Figure 1c) to visualize the CSF that has flowed out of the tagged region (Figure 1d) in dura mater into the parasagittal dura (PSD) and then to the SSS. Next, we normalized the signal difference as signal increase ratio (SIR) (Figure 2b and c), when plotted against TI (Figure 2d), provided real-time perfusion curves demonstrating the CSF flow. The perfusion curve which was fit to determine

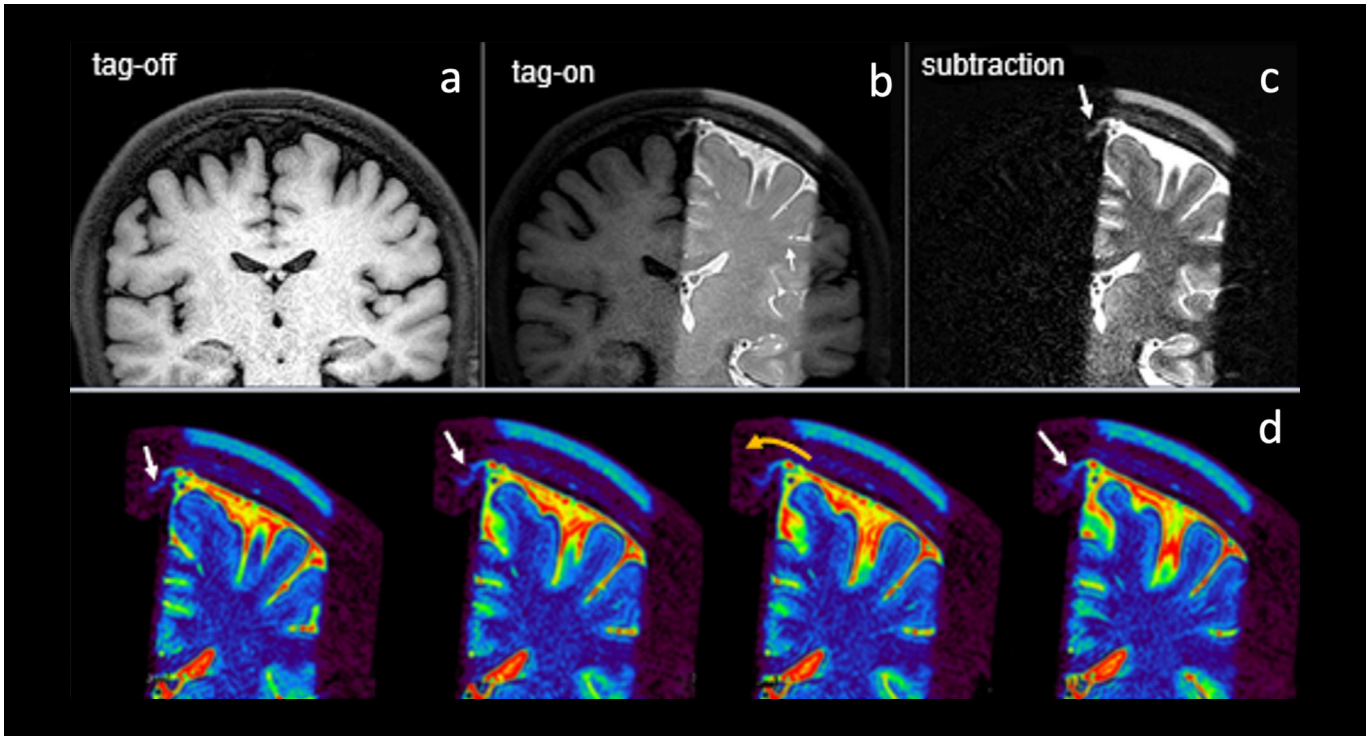

Figure 1: Tag-off (a), tag-on (b), and subtraction (c) images obtained at TI of 1500 ms. The subtracted image shows fluid moved out from the tagged region. (d) Enlarged color images of 3D volume images. Note that various slices of 3D images show fluid moved toward parasagittal dura and superior sagittal sinus.

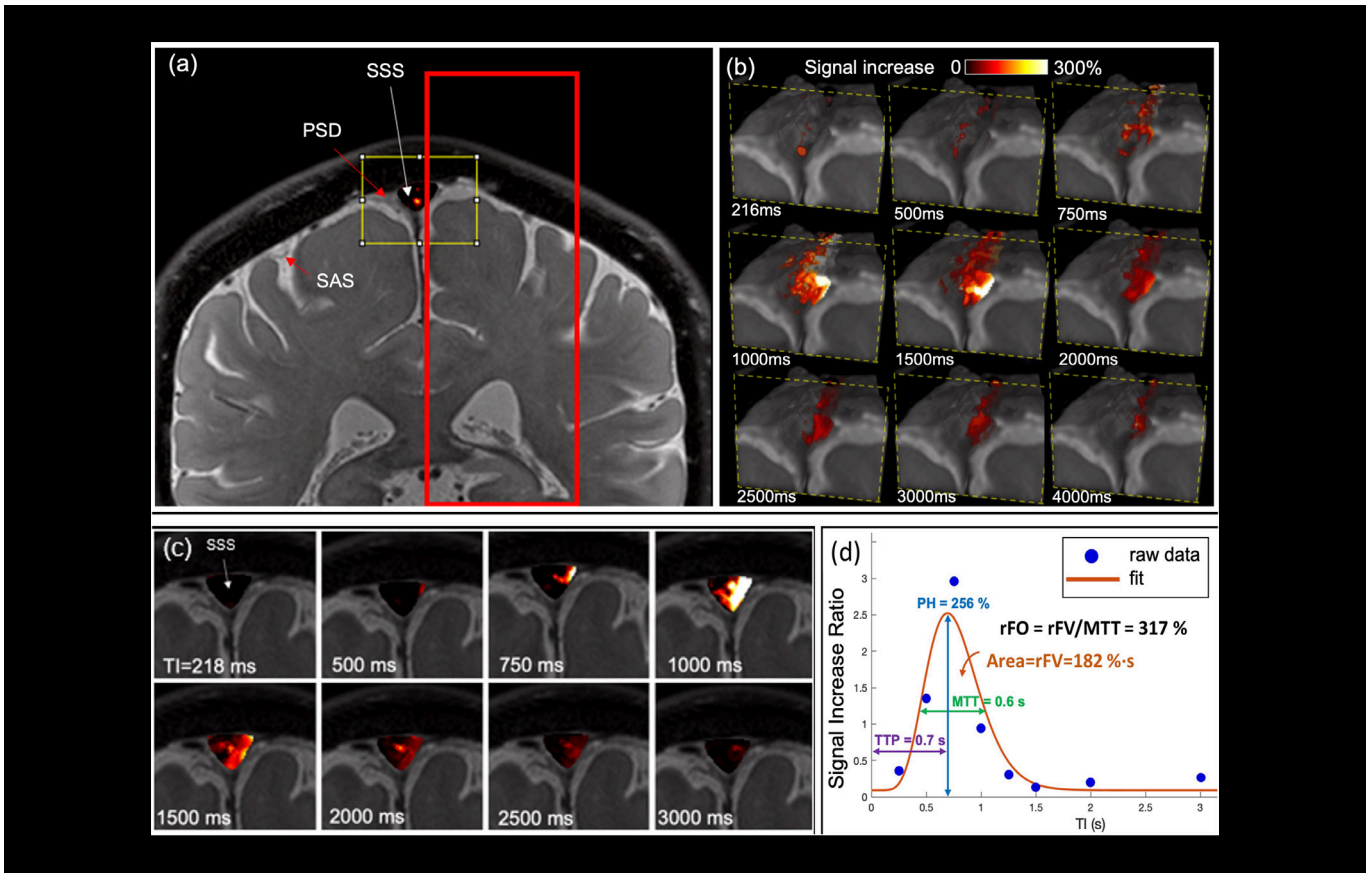

Figure 2: a) Coronal 3D cSSFSE image with a spin labeling tag pulse (red box). The Time-SLIP tag pulse is placed about 10 mm away from the superior sagittal sinus (SSS). b) A series of oblique 3D spin labeling images with various inversion times (TIs) fused over 3D cSSFSE image, enlargement of yellow box in a). Note that the tagged signals increase from the Time-SLIP on the left brain at the parasagittal dura (PSD) region at TI of 500 ms and then disappear or egress into the SSS by 1500 ms. c) Straight coronal fusion images of tagged MRI signals around the SSS region over 3D cSSFSE images at various TIs show tagged fluid outflow from the tag pulse to dura mater and PSD into the SSS. d) Tagged CSF outflow signal at the SSS. Circles show the data points, and the line indicates the curve fit. Peak height (PH) is 256%, mean transition time (MTT) is 600 ms, time to peak (TTP) is 700 ms, relative fluid volume (rFV) is 182 %·sec, and relative fluid outflow (rFO) is 317 %, obtained by dividing rFV by MTT.

quantitative glymphatic flow metrics such as peak height (PH), mean transit time (MTT), time to peak (TTP), relative fluid volume (rFV), and relative flow outflow (rFO) as shown in Figure 2d. We compared the differences in glymphatic metrics between Young and Senior healthy subjects statistically. rFV and rFO were calculated using a software program developed by the authors.

Results

Direction of glymphatic outflow: For CSF outflow imaging, the subtraction images show movement of the tagged fluid out from the tag pulse area (Figure 1c). Increasing the inversion recovery time (TI) period allows the tagged fluid to travel greater distance but the signal eventually diminishes. The zoomed in area of Figure 1b image presents the tagged CSF in the dura mater, upper PSD and alongside the lower PSD. Figure 2b and 2d show the SIR color images of the at different TI, showing the direction and the length of CSF travel over time. The highest signal intensity is seen around TI of 1250 ms, followed by a decrease. We also show this at multiple coronal slices (Figure 1d), suggesting that the outflow is persistent throughout imaged slices. Figure 2b shows enlarged 3D oblique fusion images of SIR at the SSS, the upper PSD, and lower PSD in various TI periods. Bright yellow and white signal indicate high SIR values, reaching ~300%. At increasing TIs, this fusion technique captures snapshots of the egress pathway and magnitude of CSF from dura mater into SSS, alongside the PSD. Magnified coronal single slice views in Figure 2c demonstrate tagged CSF at the level of the PSD entering the lumen of the SSS from 500 to 1000 ms.

Quantification of glymphatic flow: Figure 2d shows the curve of SIR vs. TI, and the curve fitting to determine flow metrics. Sharp early peak followed by a decrease to nearly zero. To determine the effect of age on the outflow of tagged fluid measures, we compared glymphatic flow metrics in Young vs. Senior subjects. From a scatter plot in Figure 3a, the relationship appears to be non-linear, with a greater decline of rFO among Senior subjects. Spearman's rank-order correlation was applied to determine the relationship between rFO and age, which was statistically significant ($p<0.0001$). Figure 3b shows age group differences in the SIR vs. TI curves when the entire meninges were considered; Young subjects on average had greater peak height and wider curves. When comparing quantitative glymphatic metrics, PH, rFV, and rFO were significantly lower in Senior subjects compared to Young (each $p < 0.01$), as shown in Table 1.

Summary

We demonstrated a novel non-invasive MRI technique identifying intrinsic fluid clearance pathway and observed an age-related decline of CSF flow metrics in healthy subjects. Our work provides a new opportunity to better understand the relationships of these CSF clearance pathways and metrics in humans safely, which may ultimately provide insight into the prevalence of neurodegenerative diseases.

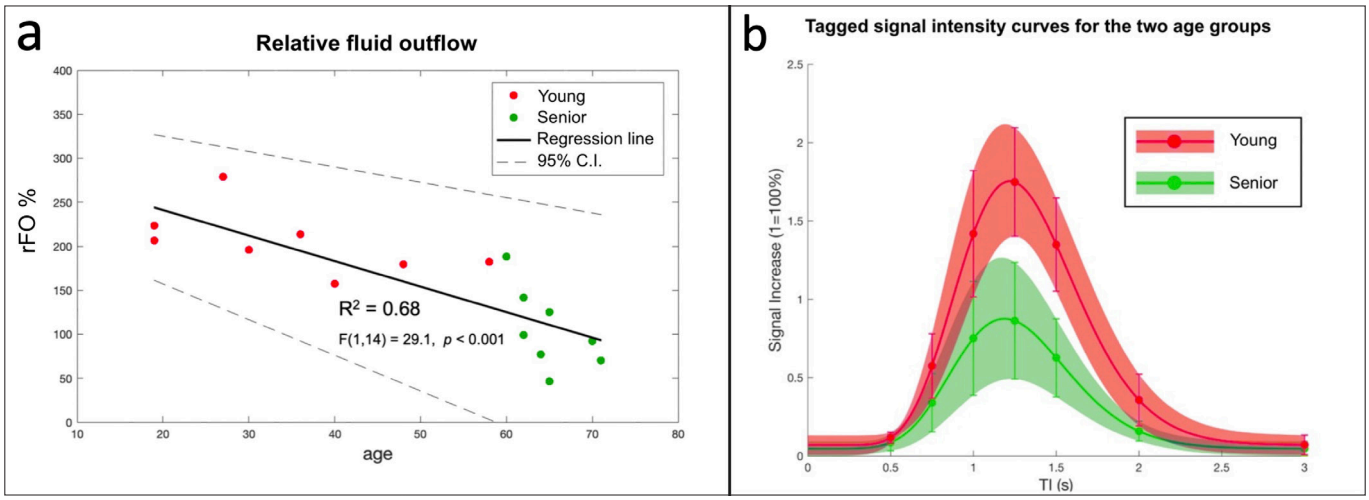

Figure 3: a) Age-related decline of intrinsic fluid outflow. b) Time-resolved curves of Young (<59 years old) and Senior (>60 years old) groups.

Group	Gender	Age	PH%	TTP ms.	MTT ms.	rFV% s	rFO%
Young	6M + 2F	31.3 ± 10.8	180.9 ± 36.2	1226.3 ± 99.3	830.1 ± 45.8	170.1 ± 32.3	204.7 ± 36.6
Senior	4M + 4F	64.9 ± 3.9	90.5 ± 39.4*	1192.5 ± 120.7	820.1 ± 37.8	86.0 ± 36.7	105.1 ± 45.2*

Table 1: Quantitative fluid outflow measures between the Younger and Senior groups. Peak Height (PH), relative fluid volume (rFV), and relative fluid outflow (rFO) show significant differences between the two groups.

* Significant difference ($p<0.001$) from young

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