

# NOVEL WATER EXCHANGE MRI SHOWS REGIONALLY INCREASED AQUAPORIN ACTIVITY IN ALZHEIMER'S DISEASE

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## Introduction

Water exchange between tissue compartments reflects the water permeability of their boundaries and their surface area. Exchange across membranes is facilitated by aquaporin channels such as AQP1 that is highly expressed on the outer surface of the choroid plexus and AQP4 that densely lines the walls of para-vascular spaces formed by astrocyte end feet. Reduction of AQP4 associated glymphatic transport has been hypothesized to contribute to accumulation of amyloid in Alzheimer's Disease(AD). On the other hand, elevated AQP4 in tissue[1] and in CSF[2] have been observed in AD. A noninvasive method to probe aquaporin mediated exchange could provide insights into the pathology of AD and other brain disorders.

We previously demonstrated that T2 based labeling can be used to image water exchange at the choroid plexus and within tissue fluid boundaries of the cortex. [3] Here, we have employed a further optimized method to evaluate changes of water exchange in patients with AD in comparison to healthy aged-matched controls.

## Methods

21 subjects with MCI or mild to moderate AD and 16 age matched healthy controls were imaged following a protocol approved by our institutional IRB and with written consent from the subjects, and a legally authorized representative if appropriate. Imaging was performed using the previously described water exchange imaging on a GE Signa Premier XT 3 T scanner and the vendor's 48 channel head coil.

Imaging Method: Water exchange imaging was performed with a new approach that selectively attenuates the magnetization in tissue, where T2 is shorter, and then observes the reduction of longer T2 signal within CSF and paravascular spaces caused by water exchange. Since water exchange across membranes is greatly facilitated by aquaporin channels, it is expected that the resulting exchange signal will primarily reflect aquaporin activity.

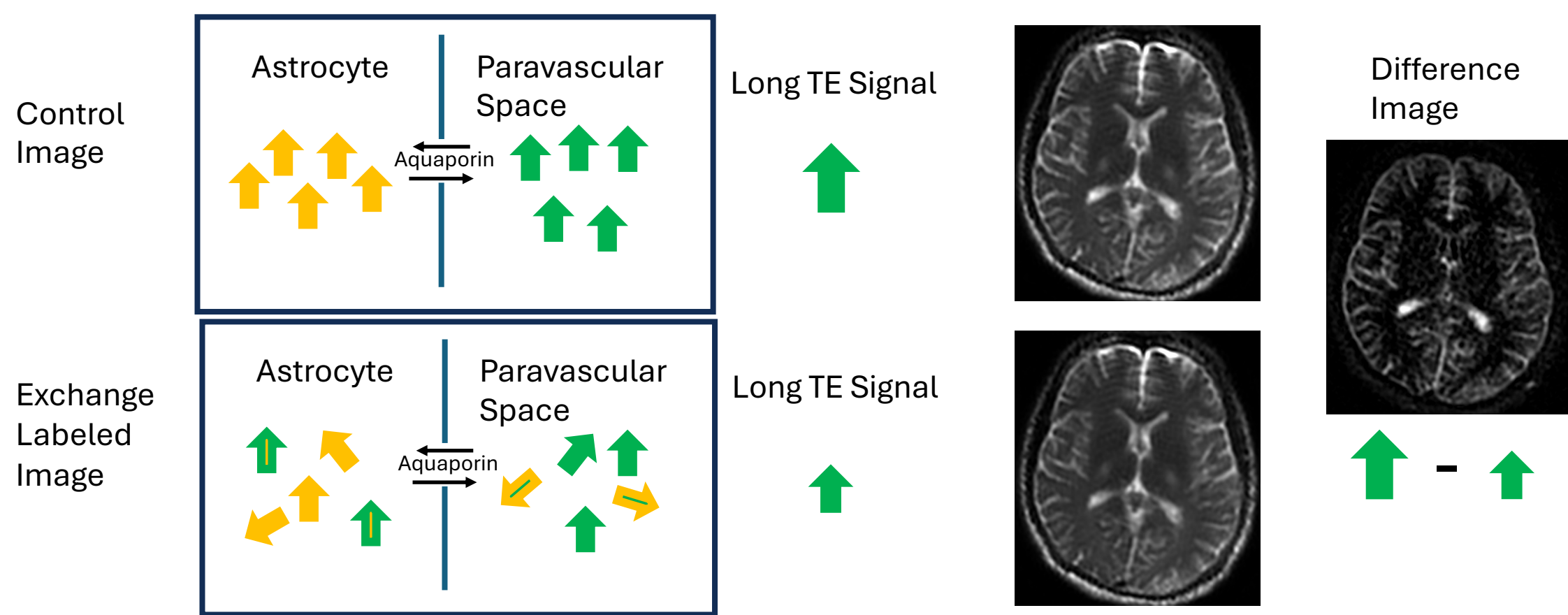


**Figure 1:** Conceptual schematic of the water exchange imaging method. Tissue magnetization with shorter T2, such as within astrocytes, is selectively attenuated by a saturation sequence with long duration. Attenuated magnetization passes through aquaporin channels into the fluid spaces, such as the paravascular spaces, where it reduces signal on long TE images. The difference between the saturated and unsaturated images reflects water exchange.

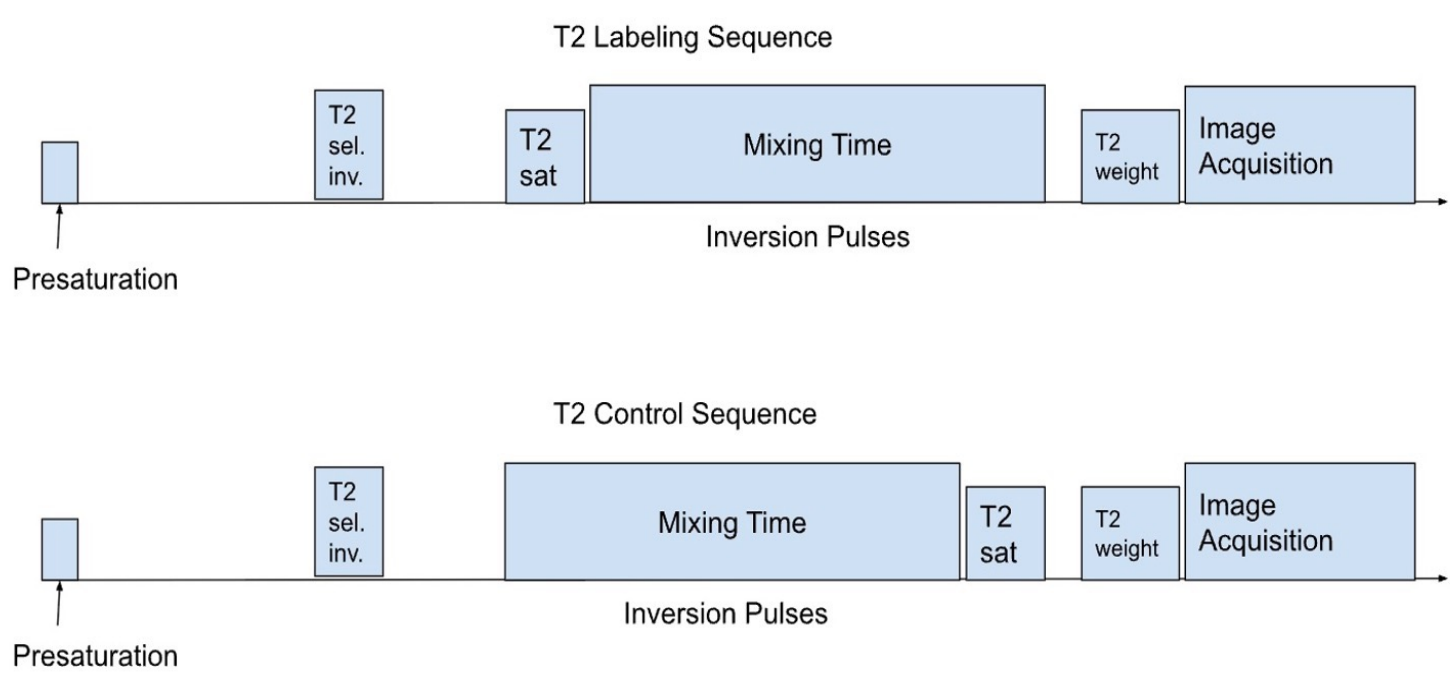


**Figure 2:** MRI sequence timing diagram for practical water exchange sequence. Shifting the order of the T2 saturation and the mixing time for the control is an effective method to remove systematic effects unrelated to water exchange[3].

## Results

Exchange images were quantified as the ratio to reference images and transformed to stereotactic space for further analysis with Statistical Parametric Mapping. Images showed highest signal in the choroid plexus, consistent with AQP1 mediated exchange, and within the cerebellar and cerebral cortices, consistent with AQP4 mediated exchange. Elevated signal was also observed in some subarachnoid cisterns, but CSF flow related noise in these regions reduces confidence in this signal. (Technical improvements have since greatly reduced this flow related noise)

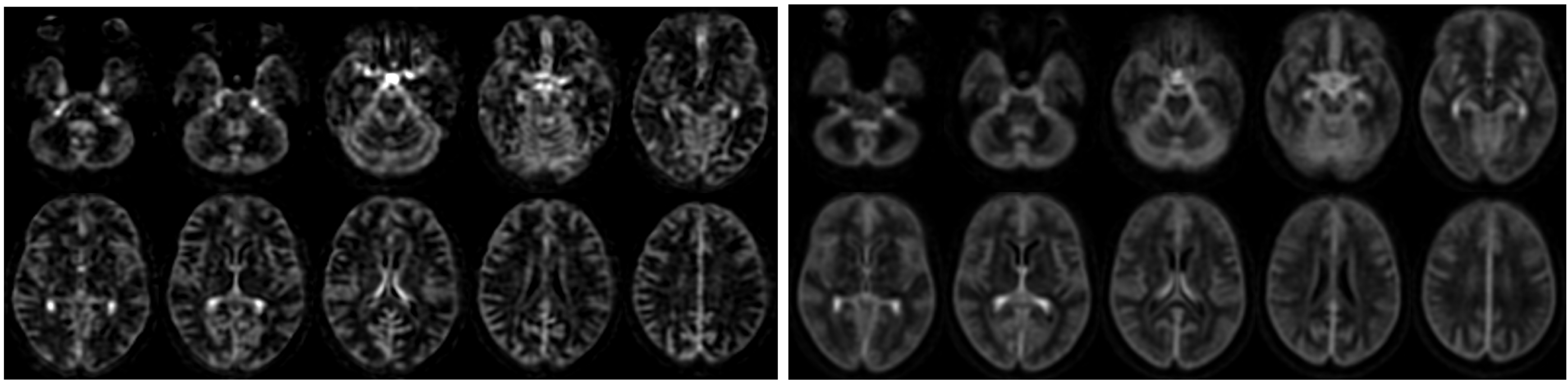


**Figure 3:** Representative water exchange images from a 68 year old healthy volunteer, left, and the average of the 16 healthy elderly controls for this study. right.

Comparison of patients and controls shows an increase in water exchange in lateral and medial temporal cortex, orbitofrontal cortex, and lateral parietal cortex within patients. This would indicate elevated AQP density and, if AQP4 and glymphatic functionally are mechanistically related, elevated glymphatic function in AD. This pattern may indicate elevated aquaporin density or altered aquaporin-mediated exchange. If AQP4-related exchange and glymphatic transport are mechanistically linked, these findings may reflect compensatory or disease-related changes in water exchange in AD.

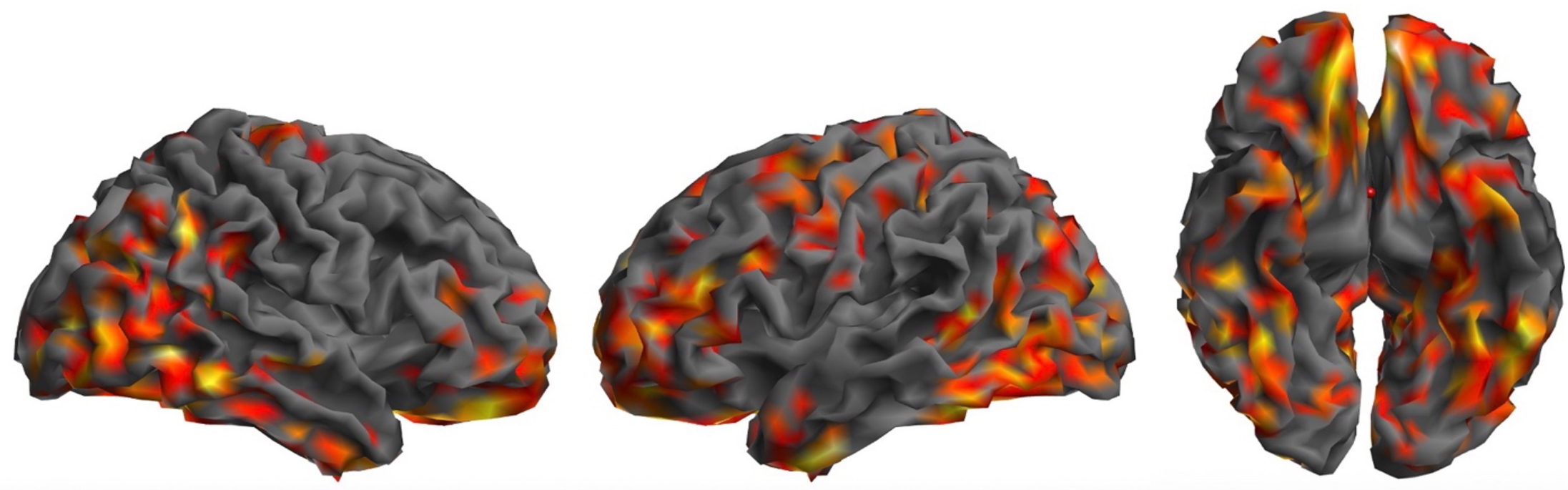


**Figure 4:** Regions of significantly increased water exchange in 21 AD patients compared with 16 healthy elderly controls. Voxel  $p < 0.05$  and cluster correction for  $p < 0.02$  were employed within SPM25. Elevated exchange is consistent with reported measurements of increased AQP4 in CSF and tissue.

## Discussion

These findings suggest that water exchange MRI may provide clinically meaningful information about brain fluid regulation in AD. With further validation, this technique could complement conventional structural MRI by offering a noninvasive marker of tissue-level fluid exchange, with potential applications in monitoring disease progression and evaluating patients receiving anti-amyloid therapies, including those at risk for ARIA.

## Acknowledgements:

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## References:

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