Beyond perfusion: measuring water transport across brain barriers with arterial spin labeling MRI

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Chapter

General Discussion

6.1 IMPLICATIONS FOR BRAIN CLEARANCE

The results of our work in Chapter 3 on measuring ASL signal in the CSF were received with both skepticism as well as enthusiasm. Specifically, the discovery of blood-to-CSF water exchange outside of the choroid plexus was not expected, as this was not observed in the previous study using a similar technique in mice.[47] This work created a bit of a stir in the brain clearance neuroimaging community and a healthy amount of discussion was had each time these results were presented in conferences.

The spatial extent of the signal and the comparable exchange time values between the choroid plexus and the subarachnoid space lead us to believe that we may be observing CSF secretion from the arteries within the subarachnoid space. It is however not possible to affirm this with certitude without a comparable brain-wide measurement of reabsorption of water from the CSF back into the blood, to establish the net flow of water across the BBB. The combination of BBB and BCSFB imaging in Chapter 5 expands this observation to the BBB by showing that there are two distinct processes occurring at the BBB throughout the brain: blood-to-tissue and blood-to-fluid water exchange.

It is worth asking what exactly is the nature of the signal that we observe outside of the choroid plexus. What is the pathway of water to go from blood to reaching larger CSF pools where it can be measured? There is the possibility that water crosses directly from blood vessels into the CSF-filled perivascular spaces which surround them and connect with the subarachnoid space. Conversely, the BBB in the capillary bed may also be exchanging fluid into the ISF, which then mixes with CSF. If the latter is the case, the intermediary step in the ISF complicates the signal. On the one hand it should make the process more time-consuming than the direct blood-to-CSF exchange of the choroid plexus, and may explain the differences in $K_{bl->CSF}$ between these regions seen in Chapter 5. We may also need to modify our exchange model to include the ISF as an intermediary compartment between the blood and CSF. The notion that the observed extrachoroidal signal may simply be coming from the ISF itself is also alluring. However, this would imply that CSF and ISF have very similar magnetic properties, in particular their T_1 and T_2 relaxation times, for the modeled signal to be classified as originating from CSF. While the chemical makeup of pure CSF and ISF makes them virtually indistinguishable, their position within the CNS does differentiate them. Measurements of the ISF T_2 are difficult, because ISF exists only in extremely small interstices between tissue cells, and cannot be imaged independently without partial voluming effects. Efforts have however been made to extract these properties of ISF from combined diffusion and multi-echo imaging and multicomponent T2 analysis.[217–220] It is apparent that the T_2 of ISF itself may be significantly shorter than CSF T_2 because of its close contact with tissue causing interactions in their magnetizations. It is therefore more likely that the

CSF-ASL signal is indeed present in larger CSF-filled spaces such as the perivascular spaces and subarachnoid space.

Our results were also consistent with the mounting evidence in the case against the current prevailing hypothesis of CSF physiology and motion: the third circulation. While we remain cautious about describing our observations as CSF secretion by the BBB, this work points in the direction of the Bulat-Klarica-Orešković hypothesis,[35] although the evidence is not yet sufficient to confirm it. In reality however, the persistence of the third circulation theory into modern day physiology is astounding considering the many challenges to every part of this theory arising from research over the last hundred years. It appears clear that CSF physiology is indeed more complex than previously thought. The adherence to the third circulation hypothesis now resembles dogma more than it does science. Amusingly, while Cushing in his 1925 lecture[26] mocked as "Galenic" the idea of an ebb-and-flow motion of the CSF, this theory is now gaining traction. In light of our results, in addition to recent studies showing the link between CSF motion and pulsatile driving forces like the heartbeat, respiration, and vasomotion, the concept of a sponge-like mixing and draining of CSF and brain waste appears attractive.

6.2 LIMITATIONS OF THE CURRENT TECHNIQUES

The techniques discussed in this work in no way form a complete and exact view of water exchange in the brain, and they present a number of limitations. Firstly, as previously mentioned, ASL only allows the measurement of unidirectional water exchange from the blood to other compartments of the brain. As a consequence, it is not possible to make conclusions about the net flow of water across the BBB and BCSFB.

Secondly, the acquisition methods presented are fairly slow, taking a full one-hour scan session to acquire a dataset for measurements of BBB and BCSFB exchange. They also are associated with low SNR, especially in the CSF where the signal is approximately 10-20% of the perfusion signal in tissue and approaches the noise floor of detectable signal. As a result, these techniques need further optimization before they can be effectively used in the clinic.

Thirdly, quantification of exchange time parameters using these techniques is imperfect. Fitting complex models with a lot of degrees of freedom is difficult, and to make this easier, we set the T_2s of the compartments to predetermined values which are the same for all subjects. However, different people do tend to have different T_2s of blood, GM, and CSF. In the case of CSF, this may not have a large impact on fitting because its T_2 is so long and so different

from other compartments that any component of signal with a large enough T_2 should be classified by the fitting process as CSF regardless of the precise value of the parameter. However, the case of the blood is particularly problematic as arterial blood has a variable T_2 not only between subjects, but also depending on oxygenation and hematocrit. Additionally, we mostly ignore the white matter in our analysis. WM has lower perfusion, a shorter T_1 leading to lower ASL signal, and a T_2 that is short and similar to that of GM, making it very difficult to properly measure WM signal and separate the two components with our analysis.

Finally, there is currently no standard of reference to compare our blood-to-CSF exchange time measurements to. Future studies are needed for validation of this parameter.

6.3 FUTURE PERSPECTIVE FOR FLUID TRANSPORT IMAGING WITH MRI

Our exciting results open up new questions for future research to answer. The most pressing issue would be to devise a method to measure the exchange of water from the CSF back into the blood, in order to extract the net flow rate of water and draw conclusions on the secretion of fluid by the BBB. Ideally, a similar MRI method would magnetically label the CSF only, without affecting blood magnetization, before measuring signal in the blood. Perhaps a velocity-selective ASL method could be used for this, although the complex fluid dynamics of the CSF would make it difficult to choose the appropriate velocity encoding gradients, and there would remain a possibility of some blood to be labeled with the CSF, especially in the microvasculature. In theory, our compartmental models for analysis could be modified to include a component of signal exchanging back into the blood from the GM and CSF, but this would be such a small fraction of the signal that it would be virtually impossible to distinguish it from the rest of the blood signal. Emerging techniques using $H_2{}^{17}O$ as an MRI tracer which does not lose signal with time in the way that ASL signal does could be leveraged for this purpose (e.g. by injecting it into the CSF), however they would require injection, and the prohibitive cost of $H_2{}^{17}O$[216,221] makes its use in humans limited. Another addition to our understanding of water exchange in the brain would be to determine the proportion of CSF that is produced at the choroid plexus in comparison to the rest of the brain. For this, vessel-selective ASL could be used to isolate the vascular supply of the choroid plexus. If such a method were devised, and we were able to measure bidirectional water exchange across the BBB and BCSFB, in combination with our research group's technique for measurements of CSF fluid dynamics, we could attain a fully non-invasive MRI method to image CSF physiology from secretion to reabsorption.

Further improvements to the acquisition methods that we proposed are needed to make imaging faster and higher quality. Additionally, quantification could be ameliorated, for example by the use of subject-specific T_2 measurements. This would be readily feasible in GM and CSF with the existing multi-echo datasets, however T_2 quantification in blood is notoriously difficult in the presence of rapid flow.

Finally, it is crucial to corroborate our findings especially in the case of blood-to-CSF exchange times with other methods. PET may be of use for this because it can employ radioactive $H_2{}^{15}O$ as a tracer, however it does not offer the possibility of distinguishing tissue water from CSF water. The techniques discussed in this work would also greatly benefit from being tested in sleeping subjects, to assess eventual differences in $K_{bl->CSF}$ driven by sleep states, and in patients with any of the numerous pathologies which affect the BBB and BCSFB.