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

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# Chapter 1

# Summary

# 7.1 ENGLISH SUMMARY

## 7.1.1 Background

The blood-brain barrier (BBB) and blood-CSF barrier (BCSFB) play crucial roles in preserving brain homeostasis and protecting the central nervous system from pathogens and other harmful products. They are also responsible for the exchange of water between the blood and the tissues and fluids of the brain. Disruptions in BBB and BCSFB function are associated with a vast array of neurological disorders as well as the aging process of the brain. Assessing the integrity of the BBB and BCSFB therefore yields important information about the severity and progression of disease. Arterial spin labeling (ASL) has the potential to provide non-invasive measurements of the exchange rate of water from blood to tissue or CSF.

## 7.1.2 Aims of this thesis

In this thesis, we aim to study the use of ASL to measure water exchange in the brain. More specifically, our goals are:

- To study and compare existing methods for the assessment of the BBB with ASL
- To develop a novel method for BCSFB water exchange measurements in humans
- To study the possibility of combining BBB and BCSFB characterization in a single protocol

## 7.1.3 Summary of results

In **Chapter 2**, we compared two existing ASL techniques for the assessment of the BBB by combining them into one sequence for simultaneous measurements. The first technique acquires ASL with and without motion-sensitizing gradients (also known as crusher gradients) which remove signal in the vasculature, thereby allowing to estimate the arrival time of water in the blood vessels and in the tissue. The second technique uses multiple echo times to separate the origin of the ASL signal in the blood or tissue based on their distinct $T_2$ relaxation times. For this study we combined both methods by adding crusher gradients with variable velocity encoding and a $T_{2prep}$ module with different effective echo times to a time-encoded ASL sequence. This sequence cycled through every combination of effective echo time and crusher gradient strength. A bi-exponential analysis of the ASL signal through the echo times for the different crusher strengths was performed to determine the exchange time of water from blood to tissue under different crushing conditions. We show that $T_{2prep}$ probes blood water deeper into the vascular tree (i.e. closer to tissue) and offers a more faithful measurement of water exchange than the crusher gradient method.

Inspired by our results with the multi-echo $T_{2prep}$ technique and studies in rodents to measure water exchange across the BCSFB using ASL with dual echo times, in **Chapter 3** we propose a novel technique for the measurement of water exchange from the blood to the

CSF in the human brain. For this we acquire multiple time points (pairs of label duration and post-labeling delay) sequentially, combined with a 3D GRASE multi-TE readout to result in 6 time points and 8 echo times. Longer echo times successfully isolated the CSF signal, showing blood-to-CSF exchange in the choroid plexus and throughout the brain. Thorough validation experiments were performed to show that the measured signal did in fact originate from labeled blood water that had traveled into the CSF. This was the first experiment of its kind in humans which could measure this exchange non-invasively by ASL and reveal the extent of water exchange outside the choroid plexus (i.e. not originating from the BCSFB).. These results have important implications for our understanding of CSF physiology and brain waste clearance mechanisms which were discussed in Chapter 6. In this study we also presented a 2-compartment mathematical model to describe this exchange which yields whole-brain maps of $T_{bl->CSF}$, the exchange time of water from blood to CSF. The value of this parameter was approximately 60s and did not differ significantly between the choroid plexus, a known site of CSF secretion, and the subarachnoid space, implying that CSF secretion may occur as a brain-wide phenomenon. However, without measurements of the rate of absorption of fluid at these sites, it is not possible to obtain the net flow of CSF and therefore we cannot conclusively posit this extrachoroidal source of CSF secretion.

The discovery of significant ASL signal in the CSF throughout the brain has implications for the quantification of ASL perfusion parameters, in particular when using partial volume correction (PVC). PVC is a type of analysis performed on ASL data to disentangle the contributions to the CBF of the gray matter (GM) and white matter (WM) signals and extract the pure GM and WM perfusion values. Traditionally, PVC assumes that signal can only come from the GM or the WM, and that CSF signal is zero. In **Chapter 4**, we remove this assumption and measure the effects of CSF signal on the results of PVC. For this, we use simulated and real datasets where we apply PVC to retrieve pure GM CBF. We find that the overall effect of including CSF signal in PVC on the measurements of pure GM CBF resulted in an average improvement in quantification of 10%. In the choroid plexus, the difference between CBF estimates with and without the CSF inclusion was much larger and averaged 30%. We concluded that CSF signal should be taken into account in PVC as it is a fairly straightforward modification to the analysis that does not require additional measurements and provides more accurate estimates of CBF, as is the objective of PVC in the first place. CSF correction was of particular importance when measuring choroid plexus perfusion, which is a current topic of interest in the field of brain clearance imaging.

With the cumulative knowledge acquired in our previous experiments, we proposed in **Chapter 5** a method for the combined assessment of BBB and BCSFB water exchange in a single ASL protocol. We reconciled the different imaging and readout parameters needed for both techniques by sequentially acquiring multiple LD/PLD pairs and combining a $T_{2prep}$

module (used in BBB measurements because of its short inter-echo spacing) with a multi-TE GRASE readout (used in BCSFB measurements to efficiently acquire longer echo times). This resulted in 5 time points and 16 echo times acquired in an interleaved manner. We also proposed and compared 2- and 3-compartment models to fit to this data. We found that the proposed sequence is effective for imaging the ASL signal at all time points and echo times and showed signal in all three compartments studied (blood, GM, and CSF). The 3-compartment model provided a faithful representation of water exchange in the brain between blood, GM, and CSF. With it we estimated and mapped the exchange rates of water from blood to GM and from blood to CSF, $K_{bl->GM}$ and $K_{bl->CSF}$, respectively. $K_{bl->GM}$ was fairly homogenous across brain regions and averaged between 1.4 and 2 $s^{-1}$, while $K_{bl->CSF}$ showed more contrast between the choroid plexus (1.5-2 $\times 10^{-2}$ $s^{-1}$), the subarachnoid space (1.2-1.6 $\times 10^{-2}$ $s^{-1}$) and the white matter (1-1.4 $\times 10^{-2}$ $s^{-1}$). This was the first proof-of-concept of the use of a single imaging protocol for combined BBB and BCSFB assessment in the human brain.

### 7.1.4 Conclusions

In conclusion, the studies contained in this thesis provided important insight into ASL techniques to measure water exchange in the human brain. We showed that multi-PLD, multi-TE ASL is effective in characterizing both the BBB and the BCSFB and that with judicious optimization of imaging parameters, the two could be combined into one imaging protocol. This represents an important step in furthering our understanding of water exchange in all its forms in the brain and bridging the gaps in our knowledge of brain waste clearance mechanisms.