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Chapter I

General Introduction and Outline
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Since arterial spin labeling (ASL) was first proposed in the 1990s (1,2), it has developed rapidly to become one of the most commonly-used tools to study perfusion in the brain (3) as well as in other organs (4–8). This can be attributed to unique advantages such as its non-invasiveness (1–3), good reproducibility (9–12), accurate quantification (13–15), as well as its general versatility (16–24). Though expert consensus on ASL-MRI has been reached, and it has been widely applied both in research and clinical environments (25), improvements are necessary to tackle the limitations of conventional ASL-MRI, including long scan-times and a low signal-to-noise ratio (SNR). The main goal of this thesis is to further improve the ASL methodology for cerebral perfusion imaging by means of technological development. In this thesis, several new ASL techniques are proposed, which cover the full breath of ASL-methodology, thereby enabling or improving the detection of different aspects of cerebral hemodynamics. For example, conventional whole-brain territory mapping, using either planning-free vessel-encoded pseudo-continuous arterial-spin-labeling (VE-pCASL) or multiple acquisitions of super-selective pCASL, take approximately 5 min, which is frequently considered too long for standard clinical protocols (26–30). In chapter II of this thesis, vessel-encoded dynamic ASL (VE-DASL) is proposed to achieve cerebral flow territory mapping within 30 seconds, aimed specifically at the acute clinical setting. The main concept behind VE-DASL is to create a continuous inflow of label/control blocks with different encoding patterns for each feeding artery. This approach leads to continuous and unique signal fluctuations within each flow territory, thereby enabling accelerated identification of flow territories. For this new technique, different settings such as the flip angle, labeling block duration, labeling configuration and scan duration were optimized. Validation was performed by comparing the territory maps acquired by VE-DASL with the ‘gold standard’ reference maps obtained from traditional vessel-encoded pCASL.

White matter (WM) perfusion has great potential as a physiological biomarker in many neurological diseases (31–33). However, studies of cerebral blood flow (CBF) in WM by ASL-MRI are relatively scarce due to particular challenges associated with WM-CBF measurements, such as significantly lower perfusion and longer arterial transit times as compared to gray matter (GM) (34–36). Recently, ASL with a spectroscopic readout was proposed to enhance sensitivity to measure WM perfusion (37). But this approach suffers from long acquisition times especially when acquiring multi-phase ASL datasets to improve CBF-quantification. To detect multi-phase white matter perfusion in a highly time efficient manner,
time-encoded pseudo-continuous ASL (19,22) with a single voxel PRESS (Point-RESolved Spectroscopy) spectroscopic readout (te-pCASL PRESS) was implemented. In addition, a study to investigate whether the temporal signal-to-noise ratio (SNR) would increase by using a spectroscopic readout instead of a conventional imaging readout (te-pCASL EPI) was performed, as described in chapter III.

Intravoxel incoherent motion imaging (IVIM) is another non-invasive MRI technique to measure perfusion (38,39). The basic assumption of IVIM is that the blood flow in capillaries, also known as cerebral perfusion, can be considered a pseudo-diffusion process due to the random orientations of vessels within the capillary network. Traditionally, a two compartment IVIM model is employed to separate the contribution of perfusion from diffusion effects: a slow compartment in which the signal decays slowly as a function of diffusion weighting (i.e., b-value) and a fast compartment where the signal drops much faster as a function of b-value due to the pseudo-random capillary blood flow. The main concerns of the validity of this model are that a distribution of velocities as well as non-random orientation could result in more complex relationships than this bi-exponential assumption. Doubts on the validity of the IVIM approach have arisen for example from the reported ratio of gray and white matter CBF with IVIM, which are frequently much lower compared to values obtained from other techniques (DSC, ASL, O15-H2O PET) (40–43). To better understand the signal generation mechanisms of IVIM, it is important to be able to exclusively measure the diffusion properties of the blood pool and to do this for different parts of the vascular tree. By employing an ASL-preparation module before an IVIM readout the perfusion contribution can be isolated. In chapter IV, this approach was applied to investigate the blood signal as a function of b-values while the blood traverses through the vascular tree and it was compared to the results from conventional IVIM.

Pseudo-continuous ASL (pCASL) is now the most widely accepted ASL approach mainly due to its high signal-noise-ratio (SNR) and easy implementation on clinical MR scanners without the need for extra hardware requirements (3,17). However, to date, there is no reliable method to calibrate the labeling efficiency of pCASL perfusion imaging in a clinically acceptable manner, and usually a constant value (e.g. 0.85) obtained from simulations is adopted. However, variation in labeling efficiency is thought to contribute to the intra- and inter-subject variability observed in quantitative ASL (11,44). In chapter V, a novel method to measure the labeling efficiency of pCASL directly was proposed by performing multi-phase pCASL imaging distal to the labeling plane.
Higher magnetic field strengths lead to increased net magnetization resulting in higher signal to noise ratio (SNR) that can be exploited to image at a higher spatial resolution or in shorter scan-times. In particular, ASL is frequently quoted as an example of a technique that will benefit most from going to ultra-high field MRI (7T and above) (45–48), because this higher baseline SNR is accompanied by a longer $T_1$ of blood and tissue, thereby providing a ‘double-hit’ improvement in SNR for ASL acquisitions at higher magnetic field strengths. In chapter VI, the longitudinal relaxation time of blood ($T_{1,\text{blood}}$) was measured at 1.5 T, 3 T and 7 T to investigate the expected gain in SNR by performing ASL at ultra-high magnetic field. For this purpose, we measured the $T_1$ of blood in the sagittal sinus by performing a non-selective inversion pulse preceding a Look-Locker EPI sequence.

Short introduction to physiological parameters relevant to ASL-MRI

The term ‘cerebral perfusion’ is used to describe the delivery of oxygen and nutrients to brain tissue by means of blood flow. In a quantitative sense, the most commonly measured parameters of cerebral perfusion are cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral vascular reactivity (CVR), and cerebral metabolic rate of oxygen (CMRO2).

Cerebral blood flow (CBF) indicates the amount of arterial blood flowing through the brain tissue in a given period of time, normally expressed in ml blood/100g brain tissue/min or ml/100ml tissue/min (49,50). So far, the majority of CBF measurements by ASL-MRI have focused on gray matter CBF (GM-CBF) which have been recognized as an important clinical indicator for diagnosis of many neurological diseases. Although white matter CBF (WM-CBF) also has great potential as a physiological marker for patients with large vessel occlusive disease (32), neurodegenerative diseases (31) and patients with multiple sclerosis (33), WM-CBF has proven to be difficult to detect by ASL and therefore ASL-studies on WM-CBF are relatively scarce (37,51–53).

CBF is tightly regulated by means of vasodilatation and vasoconstriction of arterioles and capillaries to prevent tissue damage due to hyper- or hypoperfusion. Cerebral vascular reactivity (CVR) provides information on this regulation in the sense that it probes the ability of the microvasculature to dilate or constrict in response to a physiological stimulus, for instance, vasodilatation in response to an increase of concentration of end tidal CO2 (hypercapnia).
Impaired CVR has been found to be associated with an increased risk of stroke in patients with cerebrovascular disease (54,55).

Cerebral blood volume (CBV) is defined as the percentage of blood vessels in a specific volume of tissue. It can be divided into arterial (CBVa), capillary CBV (CBVc) and venous (CBVv) blood volume, since some methods are only capable of measuring the CBV of a particular sub-compartment. CBV adaptations are an important component of CBF regulation and CBVa is generally considered more sensitive to cerebrovascular regulation than total CBV change (56,57). CBVa has proved to be a promising parameter to identify angiogenesis (58–60) as well as to detect other abnormal regions in the brain, such as ischemic regions (61,62).

Although the brain tissue constitutes only ~2% of total body weight, it receives about 15% of the cardiac output and consumes about 20% of total body oxygen. The amount of oxygen consumed by brain tissue is described as CMRO2. CMRO2 is an important parameter to quantify brain function and vitality and can be used to evaluate brain development, for example in neonates (63).

Among all the parameters above, CBF is often considered to be the most essential cerebral physiological parameter to measure and, fortunately, it is also the most feasible parameter to be measured non-invasively by ASL-based MRI techniques, which are the main topic of this thesis.

In addition to the parameters above, information on cerebral flow territories can be considered to be important in understanding the cerebrovascular status of an individual. At the base of the brain, the major arteries (the internal carotid arteries (ICAs) and the vertebral arteries (VAs) which merge into the basilar artery (BA)) feed the circle of Willis, which subsequently distributes the blood to the anterior, middle and posterior cerebral arteries enabling the delivery of blood, oxygen and nutrition to the brain (64). The territorial information can also be used to identify which particular artery is the source of emboli in acute stroke patients (65,66).
Basic MR phenomena and MRI techniques relevant to this thesis

Longitudinal and transverse relaxation (T₁ and T₂ relaxation)

Longitudinal relaxation is the process by which the net magnetization returns to its initial maximum value (M₀) along the direction of B₀. Longitudinal relaxation can be characterized by an exponential function with a time constant T₁. The T₁ value is defined as the duration for the longitudinal magnetization to regrow to 63% of the equilibrium magnetization M₀ after a saturation pulse:

\[ M_z(t) = M_0 \left(1 - e^{-\frac{t}{T_1}}\right) \]

T₁ values depend on the type of tissue and magnetic field strength (67,68), for instance, the T₁ of blood is ~1200 ms at 1.5T and ~1650 ms at 3T while T₁ of gray matter is ~1000 ms at 1.5T and ~1200 ms at 3T (46,69).

Transverse relaxation refers to the process by which the transverse components of the magnetization vector (Mxy) dephase due to spin-spin interaction. The T₂ value is defined as the time it takes for the transverse magnetization to lose 63% of its starting value. The T₂ relaxation decay can be described by

\[ M_{xy}(t) = M_0 e^{-\frac{t}{T_2}} \]

In reality, the transverse decay can be much faster due to field inhomogeneities resulting in much faster dephasing, denoted as T₂*.

Perfusion-weighted MRI (PWI-MRI)

Cerebral perfusion-weighted imaging relies on the differentiation of static tissue from inflowing blood. This can be achieved either invasively by introducing an exogenous tracer into the blood stream, a technique known as dynamic susceptibility contrast MRI (DSC-MRI) or dynamic contrast enhanced MRI (DCE-MRI). Alternatively, perfusion can be measured non-invasively by magnetically labeling water protons in the inflowing blood to create an endogenous tracer; this technique is known as arterial spin labeling (ASL). The magnetic label consists of saturated or inverted blood magnetization.
**Contrast agent based perfusion MRI (DSC-MRI and DCE-MRI)**

DSC-MRI and DCE-MRI require the injection of MRI contrast agent, which is most commonly based on the rare-earth element gadolinium encapsulated in a chelate, such as DTPA. DSC-MRI monitors the passage of the exogenous tracer through the feeding arteries into the brain tissue by dynamic $T_2$ or $T_2^*$-weighted imaging, whereas DCE-MRI employs $T_1$-weighted imaging. The MR signal changes can be converted to concentration-time curves of the contrast agent, which are subsequently used to quantify perfusion parameters such as CBF and CBV based on tracer kinetic theory.

**Non-invasive PWI-MRI (ASL-MRI):**

ASL is a non-invasive MRI technique first proposed by Williams et al and Detre et al in the 1990s (1,2). The basic concept of ASL is to use arterial blood water as an endogenous tracer. The blood water in the feeding arteries is magnetically labeled by using spatially selective radiofrequency pulses that invert (or saturate) the magnetization. Subsequently, common fast MRI readout modules, for instance EPI, are used after a certain delay to detect the amount of the labeled spins that enters the brain tissue. The delay between the inversion pulse and the readout is necessary to allow the labeled blood to reach the brain tissue. ASL usually requires the acquisition of two images, one control image without prior labeling of arterial blood water and one label image in which the inflowing arterial blood water was labeled. The difference between this control and label images provides perfusion-weighted information (Figure 1).

![Figure 1: perfusion weighted image acquired by the subtraction of control and label images.](image)

In the last two decades, the ASL community has been very active in proposing new acquisition techniques. However, ASL labeling approaches can still be grouped into three categories based on the temporal and spatial characteristics of
the labeling sequence: (pseudo-) continuous ASL, pulsed ASL (PASL) and velocity selective ASL (VS-ASL).

(Pseudo-) Continuous ASL ((p)CASL)

In CASL, a constant gradient applied in the direction of blood flow in combination with a constant RF pulse provides a flow-driven adiabatic inversion (16,70). By switching on this gradient and RF pulse for a long period of 1.5-2.5 s, a long bolus of labeled blood is created. The advantages of CASL are the strict control over the temporal width of the bolus of labeled spins and the fact that all blood is inverted at the same level of the feeding arteries resulting in similar longitudinal relaxation for all spins arriving in the imaging plane. Both features result in a straightforward quantification model for CBF. The disadvantage of CASL is the lower labeling efficiency, ~70% compared to ~98% in PASL (16,71). Another drawback of CASL is the occurrence of severe magnetization transfer (MT) effects due to the high RF power employed during the labeling. However, MT effects can be controlled by applying the same RF power during the control condition. By using amplitude modulation of the RF pulses for the control images, a double inversion close to each other results in a net zero-inversion of inflowing blood. Another solution is to place the inversion plane to the other side of the imaging plane to create symmetrical excitation of macromolecules in control and in label conditions which therefore will be subtracted out, although this will only be perfect for the central slice. Although CASL is simple to implement, many MR scanners do not permit continuous operation of the RF amplifiers, which limits its availability on clinical scanners.

Pseudo-Continuous ASL (pCASL) is a modification of the CASL approach which is easier to implement on the RF amplifiers of clinical MRI scanners, while providing increased labeling efficiency compared to CASL. Instead of a single, long RF-pulse, a large number (~1500-2500) of short 0.4-0.8 ms RF pulses are applied in pCASL in combination with a small net gradient along the direction of blood flow to create an overall mean gradient and $B_1$ similar to CASL, thereby still resulting in an adiabatic-like inversion of the inflowing blood (17,72,73). Compared to conventional CASL, pCASL has the advantage of producing less MT effect on the tissue in the imaging plane, because the gradients during the short RF pulses are much stronger resulting in a higher frequency difference between the labeling and imaging plane. However, pCASL is more sensitive to off-resonance effects. When resonance offsets occur in the inversion plane, the phase coherence between the labeling RF pulses and the magnetization of the flowing spins will be compromised, resulting in a significant decrease in labeling
efficiency (74–76).

So far, pCASL has proven to provide the highest SNR of all proposed ASL-implementations with sufficient reliability and robustness, and therefore pCASL has been recommended as the standard choice for clinical ASL studies by the ASL community and it is also the basis of most ASL techniques employed in this thesis.

**Pulsed ASL (PASL)**

In PASL, a single, short spatial selective inversion pulse of 10–25 ms is used for a large region below the imaging plane, thereby covering a large component of the feeding arteries (24,77–83). In this way a large amount of inflowing blood can be labeled to create sufficient SNR, although the temporal width of the bolus of labeled spins is in general smaller than for pCASL or CASL, and more importantly the width is unknown and needs to be estimated by, for example, acquiring multiple dynamic images after labeling or by incorporating QUIPSS-II saturation pulses to cut-off the bolus of labeled spins. The main advantages of PASL are the high labeling efficiency of ~98%, time-efficient labeling which enables multi-PLD imaging, and lower SAR because of the very short labeling module. PASL has the disadvantage of lower SNR compared to CASL and pCASL due to the limited temporal width. Furthermore, it suffers from difficulties in achieving accurate CBF quantification because the temporal width of label-bolus is unknown and depends on the exact anatomical layout of the feeding arteries.

**Velocity selective ASL (VS-ASL)**

In VS-ASL, the labeling is based on velocity rather than spatial position as used in CASL, pCASL and PASL. Generally speaking, it employs a velocity-selective labeling module which contains a flow-encoding gradient to saturate spins above a certain cut-off velocity ($V_c$). So far, three types of VS-ASL have been proposed, single VS-ASL, dual VS-ASL and acceleration selective ASL (AccASL) (21,23,84). Dual VS-ASL is an extension of single VS-ASL, in the sense that it adds a velocity-selective labeling module just before the imaging module to suppress venous spins that accelerates between the two velocity-selective labeling modules, as well as to suppress intravascular signal. The big advantage of VS-ASL is that it effectively eliminates arterial transit time effects, because label is also generated within the imaging slice. The disadvantage is the lower SNR due to the use of saturation instead of inversion for labeling, although velocity selective inversion pulses have recently been proposed (85). AccASL was proposed to label the spins above a certain cut-off acceleration or deceleration and thereby limits the venous contribution as observed in a single velocity selective module.
**Diffusion weighted imaging (DWI)**

DWI-MRI sensitizes the MR-signal to the Brownian motion of water molecules. The image contrast of DWI-MRI is therefore dominated by the differences in water molecule mobility. The DWI sequence generally consists of two parts, dephasing and rephrasing, as imposed by gradients applied in a certain direction: stationary water spins are first dephased and then rephased, while diffusing water spins are dephased, but are not completely rephased due to their motion, resulting in a smaller MR signal. The dephasing and rephasing can e.g. be achieved by a spin-echo sequence with the motion sensitizing gradients placed on both sides of the refocusing pulse, or by a bipolar gradient.

Intravoxel incoherent motion imaging (IVIM) is a particular variant of DWI techniques and the one used in this thesis. It was first proposed in 1980s to measure perfusion and diffusion simultaneously by Le Bihan et al. (39,86,87). The assumption of IVIM is that blood flow in the capillaries, known as cerebral perfusion, can be considered as a pseudo-diffusion process due to the random directions of the capillary tree. A two compartment IVIM model was used to separate the contribution of perfusion from diffusion effects: a slow compartment $D$ where the signal decays as function of $b$ values due to the Gaussian dynamics and a fast compartment $D^*$ where the signal drops faster as a function of $b$ value due to the faster moving spins in the blood flow within the capillaries ($b$ value is related to the gradient strength of the flow-encoding gradients and indicates the amount of diffusion weighting).

**Magnetic resonance spectroscopy (MRS)**

MRS is normally used to explore the metabolism and molecular composition of tissue. The main difference between MRS and MRI is that MRS provides information on physiological and chemical processes by means of spectra instead of anatomy by means of imaging. MRS depicts the chemical shift of protons thereby enabling the identification of the molecular structure. MRS spectra can be obtained from many different nuclei, but in this thesis, only water proton spectroscopy is considered, and more specifically one of the MRS methodologies called single voxel point resolved spectroscopy (PRESS) (88,89). The PRESS sequence consists of a $90^\circ$ pulse followed by two $180^\circ$ pulses. The single voxel-of-interest is selected by three spatially-selective radiofrequency pulses applied in three orthogonal directions. The spectroscopic signal will only originate from the intersection of the three orthogonal planes. PRESS has the advantage of a
relatively high SNR and minor sensitivity to motion compared to other single voxel spectroscopic readouts (90).

**ASL at Ultra-high field MRI**

ASL is frequently quoted as an example of a technique that should benefit greatly from going to ultra-high field MRI (7 T and above), because longer $T_1$ values in combination with a general increase in SNR are anticipated at higher magnetic field strengths.

Higher magnetic field strength leads to higher SNR due to the increased net magnetization. Generally speaking, the SNR increases linearly as a function of magnetic field strength. Therefore, a 7T MRI scanner has ~2.3 times higher intrinsic SNR than a 3T scanner. The longitudinal relaxation time of blood ($T_{1,\text{blood}}$) is a crucial parameter for quantification of cerebral blood flow by ASL and since it also determines how fast this endogenous tracer decays, it is one of the main determinants of the SNR of the resulting perfusion maps. An improvement of SNR at 7T MRI compared to clinical field strengths is therefore anticipated by the combined effect of higher intrinsic SNR and longer blood $T_1$. However, ultra-high magnetic field, also faces many difficulties, for instance, $B_0$ and $B_1$ inhomogeneity, lower $T_{2^*}$ values, SAR restrictions that will limit the actual achievable improvements compared to 3T (91).
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