A. SPECIFIC AIMS

The overall goal of this project is to develop new methods for quantitative measurements of cerebral blood flow (CBF) and arterial transit time (ATT), also called bolus arrival time (BAT) in arterial spin labeling perfusion studies for specific applications to support the research projects and clinical applications of the Resource Center. **Note, ATT and BAT are used interchangeable in the text and figures**. Arterial spin labeling (ASL) MRI has great promise for quantitative measurements of brain function, because the method is entirely non-invasive and can be repeated rapidly and in principle indefinitely. However, due to the small volume fraction (3-5%) of blood vessels compared to brain tissue, ASL-MRI yields an intrinsically small signal and consequently poor SNR. Recently, 3D imaging of the ASL signal has become possible, providing higher SNR efficiency than conventional 2D techniques, because data acquired at every step for image formation contributes to the ASL signal. Furthermore, 3D ASL imaging facilitates measuring the time course of the ASL signal simultaneous throughout the brain, as there is identical inflow time in all segmented 3D slices, unlike multi-slice 2D techniques. However, the development of 3D ALS techniques has been complicated by the demand for fast single-shot acquisitions while avoiding geometrical distortions and signal loss. Over the past decade, the investigator of this project has developed new 3D acquisition methods resulting in higher efficiency, sensitivity, and precision. This application to create new cycled labeling methods represents new efforts to develop improved acquisition techniques focused on the detection of neurodegenerative diseases. The specific aims of this project are:

Aim 1: Develop Dynamic ASL with multi-bolus Hadamard encoding: Resent results show ATT measured in time series ASL images may be a useful biomarker in differentiating mild cognitive dementia for Alzheimer's disease. The time coarse data is obtained by repeating the ASL measurements with incremented TI to obtain signal time curves. A novel cycled labeling scheme will encode flow changes with multiple pulsed boli within each of several cycles of ASL image acquisition. We will develop a novel method of Hadamard encoding in cycled ASL sequences to obtain many boli of shorter durations and to obtain several times higher SNR or reduce acquisition time and improved curve fitting of different vascular compartments to evaluate dynamic signal changes.

Aim 2: Development of Multiple-Echo 3D GRASE Acquisition: We aim to extend 3D ASL GRASE to dual-echo and multiple echo time (TE) acquisitions that provide the T2-relaxation parameterization of the ASL signal. To obtain this information, we will develop well controlled pulse sequences timing changes utilizing both single acquisition and multiple data acquisitions with an encoded variable TE parameter.

Achievement of the aims of this project will establish a set of protocols that can be used to develop functional imaging markers of neurodegeneration for the purpose of early diagnosis and monitoring progression of these diseases. These projects will also benefit a large number of funded ongoing collaborative and clinical research studies.

B. BACKGROUND AND SIGNIFICANCE

B.1. Measurements of Cerebral Blood Flow: Ubiquitously associated with neurodegeneration is abnormal cerebral blood flow (CBF). This view is supported by numerous functional studies using positron emission tomography (PET) or photon emission computerized tomography (SPECT) [1-6]. CBF measurements are especially useful when no specific information is evident in structural MRI [7]. Structural and CBF alterations may also occur at separate locations, which may reflect an underlying disease process, where one precedes independent of the other [8]. Moreover, several findings suggest that CBF reductions precede structural changes in some conditions [9]. For all these reasons, assessment of CBF is considered to be extremely useful for early detection and diagnosis of ND. However, classical PET and SPECT methods, which rely on radioactive tracers to measure CBF, have for clinical purposes several major disadvantages, including exposure to radioactivity, need for an arterial catheter if performed quantitatively, and limited availability compared to MRI. In MRI, paramagnetic agents inducing a dynamic susceptibility contrast (DSC) via relaxation effects are used as tracer for CBF. Although widely used to assess CBF in cerebral ischemia, DSC-MRI has rarely been employed in studies of ND [10-12]. A fundamental problem of DSC-MRI is that the paramagnetic agents are only indirect tracers for CBF, in contrast to the radioactive tracers used in PET and SPECT, and the

relationship between the DSC-MRI signal and concentration of the paramagnetic tracers is difficult to establish [13]. This makes blood flow quantification challenging for DSC-MRI. In addition, DSC-MRI suffers from a number of practical problems, notably limited repeatability and tracer residue after multiple bolus transits that further complicate quantitative measurements.

B.2. Arterial Spin Labeling: An attractive alternative to measure CBF is arterial spin labeling (ASL) [14], because the method is entirely non-invasive and can be repeated rapidly and in principle indefinitely. In ASL-MRI, CBF is measured by magnetically inverting the magnetization of water protons in the inflowing arteries using radiofrequency (RF) pulses and collecting the signal after the labeled blood water flows into the imaging region. However, due to the small volume fraction (3-5%) of blood vessels compared to brain tissue, ASL-MRI yields an intrinsically small signal and consequently poor SNR, which may explain the slow acceptance of ASL-MRI by clinicians. Recently, 3D imaging of the ASL signal has become possible, providing higher SNR efficiency than conventional 2D techniques, because data acquired at every step for image formation contributes to the ASL signal [15,16]. Furthermore, 3D ASL imaging facilitates measuring the time course of the ASL signal simultaneous throughout the brain, in contrast to sequential measurements with 2D techniques. The development of 3D ALS techniques has been complicated by the demand for fast single-shot acquisitions while avoiding geometrical distortions and signal loss. Recently, Feinberg et al. [15] developed a fast 3D mapping technique, based on GRASE [17] to tackle both problems. GRASE acquires a combination of gradient and spin echoes, thus taking simultaneously advantage of gradient echoes to accomplish fast acquisitions and spin echoes to reduce geometrical distortions and signal loss. 3D ASL-GRASE has been installed at 3T [18] and in our laboratory at 4T (see preliminary results below), showing great promise, especially for imaging of areas affected by strong magnetic susceptibility variations, such as the orbitofrontal and inferior temporal cortex. New parallel imaging methods developed in the Reconstruction Core of this application and improved distortion corrections developed in this Acquisition Core (see project by Dr. Schuff) should further improve the performance of 3D ASL-GRASE. At present, however, variable transit delays of the ASL signal coupled with dispersion of bolus duration confound quantitative measurements of perfusion, increasing intra-subject and inter-subjects statistical variation. Pulse sequences that reduce dependence on transit delays and bolus duration are imperfect and may induce artifacts in the perfusion signal [19]. In this application, we will explore using rapid (30 second or less) single shot 3D ASL images in incremental post-labeling delay series acquisitions to determine peak blood arrival time in the brain, thus accounting variable transit delays and bolus durations to improve precision of perfusion measurements. However, serial acquisitions to capture transit delays and bolus dispersion may substantially prolong scan time. We therefore aim to reduce the scan time in a repetitive dynamic process by limiting acquisition of unlabeled images to a minimal set that sufficiently captures the stationary background signal, thus reducing the total scan time with optimally no change in SNR or spatial resolution. The gain in sampling efficiency of 3D ASL-GRASE can be used in several ways, including higher spatial or temporal resolution. A high temporal resolution is especially attractive to study uptake of water into the brain.

B.2.a. Fast Imaging Sequences: There are several fast imaging sequences which have been combined with ASL including EPI, FSE (RARE), GRASE and SSFP sequences and hybrids of many of these sequences. Due to the low sensitivity of ASL technique, a fast single-shot MRI sequence can be repeated for signal averaging to raise SNR while the measurement of hemodynamics is also favorably encoded in the fast sequence. The combined physiological and encoding processes of blood flow during the image readout sequence can effect the quantitation of CBF and effect SNR as well. For example, the use of multi-slice 2D EPI is highly efficient but limited in bandwidth due to T2* decay and artifacts from susceptibility which can be avoided using spin echo based sequences. The multi-slice 2D EPI technique has slice to slice incrementally longer inversion time, or inflow time (TI) and in this respect varying blood arrival time in each slice, as well as slice dependentT1 decay of the blood signal.

The use of 3D FT sequences increases the sensitivity and SNR of the sequence due to the longer echo train and corresponding larger number of signal sampling time of each voxel (all 3D signals used). A single shot 3D sequence also has a very simple and uniform timing as the initial volume selective 90 degree excitation pulse creates a constant blood inflow time in all segmented slices, eliminating the complexity of multi-slice 2D variable in-flow time and variable T1 decay which becomes constant in all regions of the 3D image. One alternative to single-shot 3D is low flip angle segmented (multi-shot) 3D EPI sequence which has

lower SNR due to the lower flip angles and has variability of TI inversion times in k-space instead of varying in each of the 2D images. The TI varies on the segmention phase encoded axis and with FT it becomes convolved in the final 3D image.

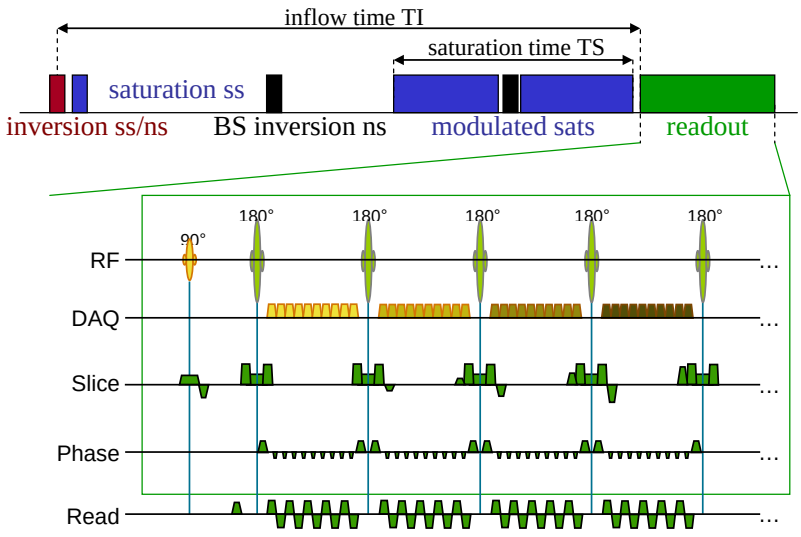
C. PRELIMINARY RESULTS

C.1. The Investigator of this Project: David A. Feinberg is an MR physicist and neuroradiologist. Dr. Feinberg has contributed to the development of quantitative blood flow imaging. He made some of the earliest time-of-flight (TOF) images of arterial blood flow [20] utilizing a multiple bolus labeling technique and earliest Fourier velocity images [21]. He made the first measurements of pulsatile brain motion and CSF velocities in the human brain [22]. He was the founder and first chairman of the ISMRM Study Group on Quantitative Flow and Motion. As the PI of an NIH RO1 grant, Dr. Feinberg led an investigation to develop optimized sub-second 3D brain imaging [23], which has led to the highly successful ASL single-shot 3D GRASE sequence which is to be applied in these investigations [15,24,25]. Dr. Feinberg has invented several fundamental techniques which are used in fast MRI pulse sequences and 3D imaging. In the 1980s, Dr. Feinberg presented half Fourier imaging [26], and the first use of partial Fourier in single-shot EPI sequences to shorten the effective TE which gave marked improvement in EPI image quality [27]. He proposed and developed other techniques including "inner volume imaging" [27] to be combined with EPI and GRASE imaging [24,25,28]. Dr. Feinberg invented GRASE which combines CPMG spin echo and EPI gradient echo techniques. He has invented "simultaneous echo refocusing" in EPI [17,29], which reduces the imaging time of DSI fiber tractography [17]. Other sequence development work includes "echo time shifting" in multi-shot EPI and GRASE to eliminate phase error artifacts, and "fly-back" k-space trajectory in EPI [15] to eliminate Nyquist ghost artifact [30].

C.2. ASL-3D GRASE Implementations

There is currently greater access to a 1.5T scanner for sequence development which is easily ported to the 4T scanner as both scanners have identical gradient systems and computer operating software. We have utilized a 1.5T scanner for pulse sequence development of ASL-GRASE with the knowledge that the sequence design is irrespective of field strength yet highly dependent on gradient performance. The Sonata cardiac Siemens scanner at 1.5T and the Varian-Siemens 4T scanners have identical gradient coil and power supply systems (40 mT/M, 200ms-M/mT slew rate). Also the same operating pulse programming software is on the 1.5T and 4T scanners. Therefore the design of new pulse sequences can be performed at 1.5T at AMRIT and ported to the 4T scanner at the UCSF facility. This relationship has led to more rapid sequence development and optimizations. On the 4T scanner, the sequences are acquired with fewer signal averages and with optimization of RF due to the increased demands RF transmitter power and associated RF heating (SAR).

Fig.1. Sketch of 3D ASL-GRASE



The single-shot 3D GRASE sequence has been combined with the labeling technique of "pulsed" ASL and pseudo continuous" ASL. A sketch of the 3D-ASL GRASE is depicted in Figure 1. Several variants have been explored with partial Fourier encoding of the slice axis for establishing earlier effective TE, as well as centric phase encoding orders. We have modified the QUIPS II [31] sequence to perform outer-volume suppression of the excitation volume for advantage of establishing a more uniform slab volume profile and outer slab boundaries which is important for maximizing

slice coverage. The standard Q2TIPS method uses off-resonance saturation pulses relative to the imaging slab to produce a single saturation band proximal to the acquired slices before the image readout takes place [32]. This allows limiting the length of the labeled blood bolus and efficiently reduces intra-arterial blood signal in the resulting perfusion images. We used modulated saturation pulses, which result in two saturation bands on both sides of the imaging slab. This not only suppresses intra-vascular blood flowing into the axial imaging slab from cranial and caudate directions, thus, also reducing the signal of most venous vessels. The image quality of the single-shot readout module can be improved by reducing the necessary oversampling in 3D encode direction to avoid aliasing.

The ASL imaging sequence uses background suppression techniques and multiple non-selective inversion pulses to null the signal of the stationary tissue, while the ASL signal remains unaffected. For a given inflow time TI the following analytical solution of the signal equations was used to null two components with T1 relaxations rates $R1_{opt}$ and $0.5 \cdot R1_{opt}$ using two inversion pulses at time τ_1 and τ_2:

$$\tau_{1,2}(TI) = TI + \frac{2}{R1_{opt}} \cdot \ln\left(\left(\frac{1}{2} \mp \frac{1}{4}\right) + \left(\frac{1}{2} \pm \frac{1}{4}\right) \cdot e^{-\frac{1}{2} \cdot TI \cdot R1_{opt}}\right) \qquad \text{(Eq. 1)}$$

For the measurements at 1.5 T an $R1_{opt}$ value of 500 ms was assumed. For an inflow time of 1800 ms the nulling of the magnetization was calculated to occur after 1700 ms to reduce artifacts due to different signs of the signal of components not matching $R1_{opt}$ and $0.5 \cdot R1_{opt}$. The positions of the non-selective inversion pulses are then 751 ms and 1471 ms after the labeling pulse. A technique related to Q2TIPS [33] was applied with multiple saturation pulses with a 40mm thickness of slab saturation using the FAIR spin labeling scheme [34]. The total inflow time was chosen to be 1600 ms with a duration TS of 700 ms. A single shot 3D-GRASE sequence is used as readout (Fig.2). Twenty-four repetitions were applied (acquisition time: 2 minutes) for images. Magnitude images after non-selective and slice-selective inversion were averaged and subtracted to yield the perfusion images. The spatial resolution of $2.5 \times 3.4 \times 5.0$ mm^3 was achieved in the single shot 3D-GRASE sequence using parameters: matrix size 128x41, reconstructed to 256x80, field-of-view 320 mm x 140 mm, nominal 18 partitions, no oversampling, partition thickness 5 mm, 5/8 Fourier encoding was used to reduce the number of measured partitions to 11, echo time TE = 41 ms, repetition time TR = 2500ms, total echo train length: 451 echoes acquired within 480 ms, inter RF-spacing = 41 ms, bandwidth = 1446 Hz, off-resonance fat-saturation pulse.

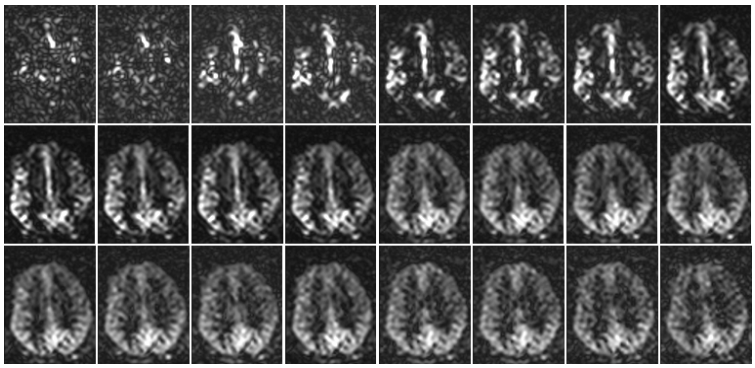
In addition to these ASL perfusion images a lower resolved time series at multiple TIs from 200 ms to 2400 ms, at 200 ms increments was acquired with a saturation time TS of 100 ms. Representative data are presented in Figure 3. The short TS of the times series is solely used to avoid infolding instead of suppressing vascular blood water signal. The time series were used to estimate BAT in each voxel of each slice. Eight repetitions per TI were applied (acquisition time: 48 s). At 1.5 T, the total measurement time of time series was 9.5 minutes. Perfusion and BAT were estimated by fitting four parameters (perfusion and BAT of micro-vascular and arterial components) of a model to the data of this times series The model function allows to separate macro-vascular from micro-vascular perfusion and consists of two components which model the arterial and micro-vascular (standard kinetic model [35]) signal behavior separately. Minimum, maximum, mean and standard deviation of the mean BAT was extracted from the maps of the micro-vascular component. The mean calculated CBF of grey matter was 60±15 ml/100g/min. More advanced modeling procedures of dynamic 3D ASL-GRASE data will be developed in the project by Dr. Schuff.

A large advantage of single-shot 3D techniques is that the whole image volume is acquired at the same inflow time and therefore the suppression pulses are optimized for the entire 3D volume rather than with slice to slice variations when using multi-slice 2D techniques. All partitions acquired throughout the echo train have the same TI for identical perfusion weighting since a 90 degree excitation is used. This fact is not hampered by the application of multiple refocusing pulses in the readout, which refocus only the existing excited magnetization captured at identical inflow time (see Fig.2). Several comparisons of image quality between ASL sequences using single-shot 3D-GRASE and multi-slice 2D GE-EPI acquisitions revealed much less distortion with the 3D-GRASE because of the higher bandwidth of the readout[18,36]. A well known increase in SNR between 2D and 3D FT imaging results directly from the larger number of signals contributing to and averaged within a voxel in 3D FT compared to 2D FT imaging. A direct measure of this difference in SNR is the square root of the total signal ADC sampling time in 2D and 3D sequences. Experimental comparison of the SNR of perfusion images showed a 2.7 fold higher SNR for 3D-GRASE ASL than 2D-EPI ASL images [18], whereas in

this particular comparison, a factor of $\sqrt{6} \approx 2.4$ was expected due to the approximately six times longer total sampling time in 3D-GRASE than in 2D-EPI readout, with total echo train durations of 430 ms vs 72 ms, respectively. There are additional factors which effect SNR changes including differences in transverse relaxation between EPI and GRASE sequence's magnetization due to the faster T2* echo train decay vs the combined stimulated echo (T1 decay) and spin echo (T2 decay) in GRASE. Early effective TE in GRASE was facilitated using partial Fourier techniques but can be further mitigated using centric k-space ordering schemes, which were not employed in these initial experiments. With intrinsically higher SNR in 3D GRASE ASL images, total scan time is reduced as fewer signal averages are required. In the above comparison assuming equal constant SNR between the two sequences, the 3D GRASE ASL sequence is approximately 6 times faster than the 2D-EPI ASL techniques. Such speed gains would hold true for any 3D pulse sequence, regardless of k-space trajectories; i.e. single shot 3D spiral-RARE [37].

C.2.a. 3D ASL-GRASE at 4Tesla: We implemented 3D ASL-GRASE at 4 Tesla and obtained preliminary results of serial 3D ASL perfusion imaging on a small number of healthy volunteers. Figure 2 depicts a time series of perfusion data from a healthy volunteer. Only one slice of 26 slices, covering the entire brain is shown. The acquisition of each 3D ASL frame took less than 34 seconds at a resolution of 4.5 x 4.5 x 4.5 mm. The entire time series was acquired in 13 minutes, with increasing TI post-labeling delays from 200ms to 2500ms in steps of 100ms. The spatial dispersion in the arrival of the ASL signal can clearly be seen in the upper row of Figure 2. Also clearly visible is the progressive disappearance of the arterial component of the ASL signal, as water diffuses into the brain. Moreover, this particular subject showed a left/right and anterior/posterior asymmetry of perfusion, as seen in the middle row of Figure 4. The significance of these preliminary data for the proposed work is that it demonstrates the feasibility to acquire multi-frame perfusion images of the whole brain in a few minutes at 4T using 3D ASL GRASE.

Fig. 2. Perfusion Time Series from 3D ASL-GRASE



C.2.b. Hadamard encoding of ASL imaging

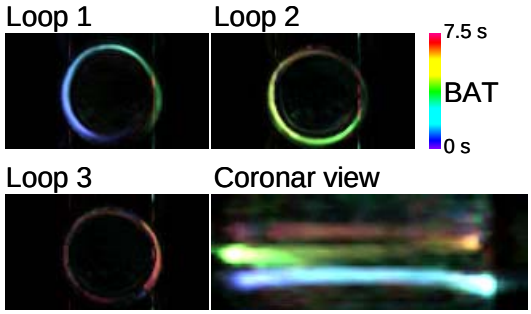
Visualization of the different intracranial vascular territories is usually obtained by using angiographic techniques. However, due to the difficulties to visualize the distal vascular bed with any angiographic technique it is difficult to infer the cortical borders of vascular territories. Arterial spin labeling (ASL) MRI provides information on cortical cerebral perfusion and by using a regional arterial spin labeling approach there is potential to visualize cortical perfusion of the anterior and posterior circulation separately. Current techniques perform the labeling in each feeding artery as a separate experiment which is extremely time-consuming. The Hadamard technique acquires all vascular territory within the same experiment without loss of efficiency. Images with different combinations of labeled arteries are combined to separate the corresponding vascular territories. A clinically useful setup is achieved by combining the regional labeling scheme with an efficient readout technique yielding a total measurement time of 2 minutes for three vascular territories with the same SNR as conventional ASL acquired in 6 minutes (41). A copy of ref (41) can be found in appendix B of this project.

In continuous ASL (CASL) the amount of labeled blood magnetization present in the imaging slab is greater than in pulsed ASL (PASL) since a labeling RF pulse is applied for a longer period of time. Therefore, in CASL the measured signal is based on a steady-state condition while it originates from a single bolus in PASL. By using more than one labeling RF pulse per cycle in PASL it is possible to increase the amount of tagged blood magnetization. A new method will be developed that enables distinction between blood magnetization tagged by a specific labeling pulse. The method allows the acquisition of time series in a very efficient way since all measured data sets are used for

reconstruction of each single time step. Therefore, a 32-fold or more reduction of measurement time is given by maintaining the same SNR level of a conventional experiment. With Hadamard matrices of size N, exactly N-1 different TIs can be encoded. Fig. 4 in the method section below shows the whole label cycling experiment for N=8. The encoding scheme based on Hadamard matrices was used to tag the magnetization of multiple blood boluses within one label cycling step. Therefore, seven different inflow times can be acquired by an eight step cycle. However, since all eight data sets in different combinations are used to reconstruct each image for a certain inflow time (only consisting of the signal of a single bolus), the SNR of each of the seven images will be as high as for a data set acquired by conventional ASL. Thus, using cycled ASL a reduction in measurement time of factor N-1 (7 in this example) can be achieved by maintaining the same SNR compared to ASL with 7 averages of the time series experiments.

To evaluate Hadamard encoding in the novel cycled labeling scheme, Fig. 3, a flow phantom experiment was performed. A flexible tube was helically wrapped around a water bottle and water was pumped through it. A single-shot 3D-GRASE sequence [15] was used for image readout (26 slices, resolution 5×5×4mm^3, acquisition time 420ms, TE 21 ms, centric reordered, TR 8s). A sixteen gradient cycle was employed (yielding 15 different inflow samples). Tagging was achieved by pseudo-continuous labeling [18] using a bolus duration of ~500 ms each. Thus, inflow times ranged from 500 ms to 7.5s. The arrival of the labeled bolus at each voxel is color coded. Three different transverse slices are shown containing different loops of the tube helix along with a coronal view.

Figure 3: Variable arterial transit times ATT (here termed BAT) visualized in phantom utilizing Hadamard encoded cycled ASL



D. RESEARCH DESIGN AND METHODS

D.1. Overview: Perfusion imaging with dynamic time series of ASL measurements will be implemented and optimized on the 4T scanner for obtaining CBF, ATT and hemodynamic parameters in patients with degenerative brain disease. The ASL 3D GRASE sequence will be developed to meet the need for i) highly reproducible quantitation of CBF , ii) scan times to ensure the best possible patient compliance.

D.1.a. Dynamic ASL with Hadamard encoding: **We have earlier introduced the new sequence design of cycled ASL used for spatial encoding multiple vascular territory [41] in which signal averaging and SNR was increased or scan time was reduced at constant SNR compared to images made with independent measurement experiments for each vascular territory. Here we propose to extend the concept of cycled sequences to improve temporal encoding and sampling inflow curves of tagged blood with higher efficiency or image SNR per acquisition time. It should be noted that this development is not an optimization of the existing PASL sequence with 3D GRASE but rather it is a new and more efficient approach to obtaining hemodynamics of tissue perfusion (40, 42). This new sequence is specifically designed to improve the measurement of perfusion and ATT changes in Alzheimer's Disease. To put into perspective, compared to our current method of sampling ATT, the proposed cycled ASL sequence would have an equivalent SNR and performed in more than an order of magnitude less acquisition time. The shorter time duration of the multiple labeling boli may improve sampling of hemodynamic time curves. In addition, we expect this approach will also improve quantitative analysis of CBF using methods developed by Drs. Zhu and Schuff in project 1 of the Acquisition Core since improved sampling of the hemodynamic time response should improve separation between the arterial and exchange phase, which is important to extract information about water exchange between the intra and extra vascular compartments.**

The basic labeling scheme is to prepare multiple blood boli for one image readout (not one bolus as in conventional PASL). The boli will be prepared subsequently and therefore have different inflow times TI_1, TI_2 … TI_N. The acquired dataset is then a mixture of the signal of all boli. By varying control

and label phase of each boli over different acquisitions with an appropriate scheme, it is possible to separate the contribution of each bolus and yield the sampled inflow of labeled blood at inflow times TI_1 to TI_N. This sampled inflow curve of the tagged blood can then be used to adjust haemodynamic parameters to an arbitrary underlying model as with conventional ASL. The preparation scheme, which was used in the experiment, is shown in Fig. 4. It utilizes Hadamard encoding to provide efficient distribution of label and control phases for each cycling phase.

The new cycled ASL can be thought of as a mixture of pulsed (PASL) and continuous ASL (CASL). Cycled ASL is not a steady state technique like CASL but instead uses multiple relatively short boli. Similar to pseudo CASL, inflowing blood is prepared over a period of time comparable to CASL. In this regard cycled ASL can be viewed as encoding the long (over 2 s) bolus of CASL and decoding it at the delivery side.

By proper selection of the preparation scheme (e.g. Hadamard encoding) it is possible to use all acquired datasets for reconstruction of each time step dataset yielding maximum SNR. As an example, acquiring a 16 gradient cycle scheme requires 16 acquisitions and reconstructs to 15 different TI time steps. This corresponds to 8 averages of a single time step in conventional ASL at the same level of SNR. Using a TR of 3.5s a complete time series can be acquired in under a minute. However, instead of using long bolus duration in conventional ASL, cycled ASL uses short boli. This might be an advantage, since perfusion modelling becomes simpler for short bolus durations. There is a potential increased temporal resolution in the sampling the rate of change of hemodynamic parameters, including tissue arterial transit times, without a SNR drop.

Use of cycled ASL in human studies needs evaluation with possible cardiac triggering to minimize errors from pulsatile flow. Cardiac gating may not be required, however, constant heart rates may be required since the preparation phase extends over multiple heart beats. Experiments will be performed in normal volunteers. Cardiac rhythm will be monitored using the physiological gating devices of the 4T, which records ECG (or EKG) for triggering scan sequences. Comparison of measurements in subjects with tachycardia and bradycardia will be evaluated for variations in perfusion quantification.

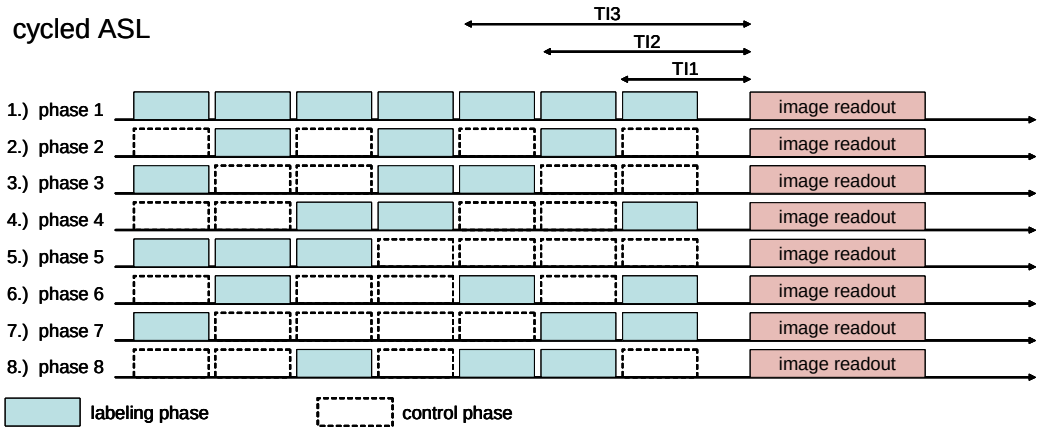


Fig. 4 Labeling and control phases for an eight-phase cycle: Seven boli are produced at different times before image acquisition (corresponding to inflow time TI). One data set is acquired for each phase consisting of different combinations of label and control preparation for separate bolus. The preparation scheme uses Hadamard encoding. All acquired data is used for reconstruction of each time step yielding most efficient SNR per measurement time.

D.1.b. Multiple TE Echo Times: The 3D GRASE which is essentially a spin echo dependent imaging sequences will be modified in time series to be used to evaluate the compartment exchange of perfused intravascular component of blood with the brain parenchyma, as described in the analysis method. We will acquire a “double echo” sequence which has an early and late effective TE by essentially dividing the echo train into two using redundant phase encoding to acquire two identical data sets but with different TEs. A different method of obtaining different TE images will be performed by repeating the imaging experiments with variable TE, using the current rapid scan times of less than 30 seconds on the 4T scanner. A ‘sliding’ echo train will be obtained by placing dummy RF refocusing pulses in the GRASE sequence between which no

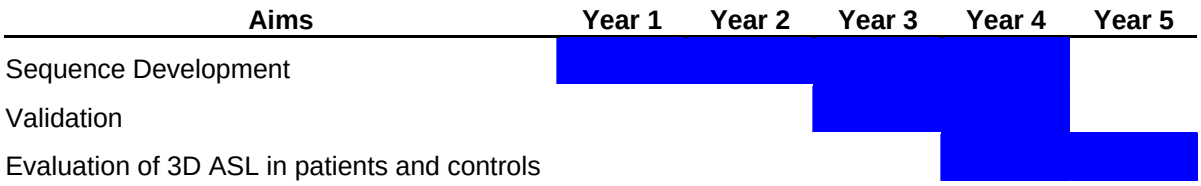
signals are acquired yet the CPMG timing is maintained. Incremental changes in the number of dummy RF periods will be applied in each repeated imaging experiment to accomplish a net effect of 'sliding' the data acquisition period and the effective TE to incremental delays to sample specific regional brain tissue signal changes due to the magnetization decay curve with variable T2 weighting. Changes in T2* weighting can be obtained by changing the k-space order between each RF refocusing period. For minimum T2* dependence in conventional GRASE, the ko encoding occurs at the spin echo time in the center of the RF pulse interval. To obtain increased amount of T2* weighting within the images, the ko and lower spatial frequency encoding can be moved incrementally off center from the spin echo time. Partial k-space acquisition will facilitate this asymmetric k-space encoding for T2* weighting. **Quantitation of T2/T2* changes of labeled water in different tissues, i.e. gray matter, white matter, arteries, capillaries and veins, can be extremely valuable for studies of water uptake in brain tissues and for more accurate CBF measurements (See section D 2.2. of project 1 in the Acquisition Core by Dr. Schuff)**

D.1.c. Optimization of ASL on normative controls and patients: We will obtain in vivo measurements in ASL time series to determine changes in arterial transit time and obtain corrected optimized perfusion phase images in different age groups of normal people to establish normative controls for the degenerative brain disease studies. The normal subjects will be grouped into 6 different age groups at 10 year increments beginning from a 20-30 year age group to 60-70 year old group using 10 normal volunteers per age group. The time series of ASL images will be repeated using different spatial resolution images. A comparison in A time series using 10 to 20 inversion times to evaluate BAT will be obtained for each sequence at 100ms to 50 ms TI increments, respectively. A comparison of calculations of CBF and arterial transit time (ATT) will be performed for each study to evaluate what sequence speed can be used optimally for patient compliance and accurate hemodynamic measurements. To this end, initial testing of the new sequences may be performed to compare conventional time-series acquisitions to the new cycled Hadamard encoded sequence (10 subjects) and on different dates (2 days) on 10 subjects. Results will be evaluated for effects of reproducibility of perfusion and BAT measurements, both short and long term variability effects of patient motion and compliance within the scanner. We will also study a subset of controls and patients with both single and multi-echo 3D-ASL GRASE to determine the value of multi-echo acquisitions and the feasibility to detect systematic differences between groups in water uptake into the brain. Performance comparisons of ASL-MRI methods will be evaluated by means of quantifiable measures, such as image texture analysis [38,39], reliability and reproducibility, and effect sizes (difference of group means / pool standard deviations). To determine precision (systematic errors) and reliability (random errors), we will study volunteers twice to allow separating between subjects from within-subject effects and noise based on linear mixed effects models.

D.1.d. Evaluation of Perfusion Acquisition in Patients with Neurodegenerative Diseases: Testing will be performed to assess the compatibility of the imaging sequences for patient scanning and the reproducibility of the perfusion measurements. For evaluation in patients with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, evaluations will be performed by the collaborative projects of the Center.

D.2. Validation: For validation, these data sets will be used by projects of Reconstruction Core for tests of using prior information.

D.3. Timeline of the Work plan



D.4. Interactions with other Projects

D.4.a. Interactions with other TRD projects: This project will mainly interact with Dr. Schuff's perfusion modeling project and Dr. Matson's MRI simulation project, both in the Acquisition Core, as well as with Dr. Liang's and Kornak's projects of non-fourier reconstruction in the Reconstruction Core and Dr. Studholme's project on image registration in the Image Processing Core.

The interactions with Dr. Schuff's project will primarily concern quantification of the hemodynamics of perfusion, including absolute quantification of CBF and estimation of arterial transit times. The interaction with Dr. Matson's projects will primarily concern optimization of B1-insensitive RF pulses for GRASE. The interactions with Dr. Liang's and Dr. Kornak's project will focus on Bayesian reconstruction of ASL-GRASE data for better spatial localization of perfusion. The interactions with Dr. Studholme's project will mainly concern accurate registration of perfusion data to anatomical MRI, which will be important for better spatial localization of the perfusion signal by Bayesian reconstruction.

D.5. Interactions with collaborative projects:

Since perfusion measurements play an important role in imaging of neurodegenerative diseases, this project will have strong interactions will all collaborative projects. However, the interactions will be particularly strong with the Epilepsy study by Dr. Laxer, the FTD study by Dr. Miller, prediction of cognitive decline study by Dr. Weiner, and the Amyloid study by Dr. Jagust,. For the epilepsy study, improved measurements of CBF are expected to benefit seizure localization. For FTD and prediction of cognitive decline, CBF is expected to improve detection of early brain dysfunctions associated with FTD. Improved CBF measurements are also expected to greatly benefit accuracy to predict cognitive decline which is studied by Dr. Weiner. Lastly, for the PET amyloid study, improved CBF measurements are expected to improve the understanding of links between amyloid deposition and hypoperfusion.

E. HUMAN SUBJECTS RESEARCH

E.1. Protection of Human Subjects: A "protection of human subject" section has been written for the entire application in the main introduction section

F. VERTEBRATE ANIMAL: N/A

G. SELECT AGENT RESEARCH: N/A

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