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Neurodegenerative Diseases

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| <b>13. ABSTRACT (Maximum 200 Words)</b><br>The overall long-term goal of imaging research to be performed with this 4 Tesla Siemens/Bruker MRI system is the development of improved diagnostic methods for accurate detection of neurodegenerative disease and responses to treatment. The 4T MRI system was installed and accepted at the end of December last year.<br>During the past months, our physicists mainly focused on developing and testing new imaging sequences and on implementing a comprehensive imaging protocol to acquire pilot data on healthy volunteers and patients. The main research accomplishments were successful implementation of several key imaging techniques, especially high resolution structural MRI to study hippocampal subfields and volumetric arterial labeling perfusion MRI to measure brain function. Data obtained on a limited number of healthy volunteers (n=49) and a few patients (n=15) indicate that the system performs within specifications and provides by far superior MRI quality than low field MRI systems. However, the gain in sensitivity to detect neurodegenerative disorders needs to be determined on more subjects. Our plans for the coming year are to study more subjects with the protocols currently implemented. In addition, our physicists will continue developing and refining perfusion, diffusion, functional, and susceptibility weighted imaging techniques and improving tools for data processing. |                                                                 |                                                                |                                                                               |                                 |
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## INTRODUCTION

The Siemens 4 Tesla MRI scanner is a state-of-the-art imaging system fully dedicated to study neurodegenerative disorders of the brain, including Alzheimer's disease, Parkinson's disease, Posttraumatic Stress, and Gulf War Illness. The system was installed and accepted at the end of December last year. Two major upgrades were recently installed which included a high power shim power supply for better field homogeneity and an 8 channel receiver head coil for parallel imaging.

During the past months, our physicists mainly focused on developing and implementing a comprehensive imaging protocol to acquire pilot data on volunteers and patients for support of new grant applications and development of novel imaging sequences. The imaging protocol focuses on: 1) structural MRI with very high resolution to measure subfields of the hippocampus and anatomical details of other brain structures, utilizing improved signal-to-noise at 4T; 2) arterial spin labeling (ASL) MRI to measure non-invasively cerebral blood flow, utilizing improved sensitivity of ASL at 4T; 3) single voxel 1H MR spectroscopy to measure accurately cerebral glutamate and glutamine in addition to other metabolites, utilizing the increased spectral resolution at 4T; and 4) diffusion tensor imaging to measure ultrastructural alterations of white matter fibers. We designed this protocol with focus on improving detection of structural, functional, and chemical alterations in the brain to improve accuracy in studying brain abnormalities in various neurodegenerative diseases. Furthermore, we started a pilot project on patients with cerebral stroke, who enter a rigorous program for physical therapy, to test if high resolution MRI can detect brain recovery after stroke and predict therapy outcome. Taken all projects together, we scanned about 64 subjects on the 4T scanner within the past 10 months. A breakdown by project of the number of subjects scanned is given in the table above (Table 1).

**Table 1**

| <b>Breakdown of Subjects Scanned on 4 Tesla*</b> |           |
|--------------------------------------------------|-----------|
| Dementia Project                                 | 6         |
| Development                                      | 49        |
| Epilepsy                                         | 5         |
| Cerebral Stroke                                  | 4         |
| <b>Total</b>                                     | <b>64</b> |

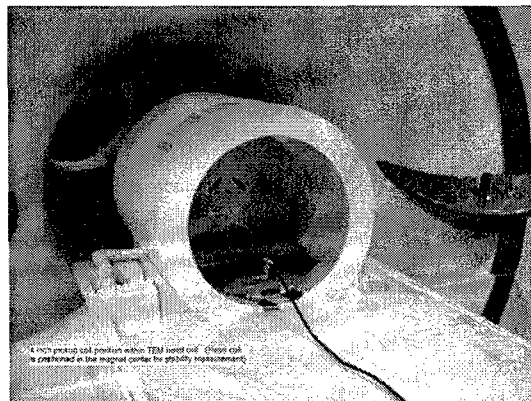
\*1/04-9/04

## BODY: PRELIMINARY RESULTS

### A. Electronic Tests of System Performance

**A.1. Radio Frequency (RF) shielding:** The relocatable building for the Bruker 4.0 Tesla MedSpec system was manufactured by PDC Facilities, and the magnet room was specified to provide 80 dB of attenuation at 170 MHz. However, the RF door leading into the magnet room did not initially meet specification tests, and only after consider re-work by the PDC Facilities engineer was it able to pass the test for 80 dB of attenuation. Because the door was considered a possible weak link in the RF shielding of the magnet room, the door has been tested periodically for RF leakage. The tests are done by transmitting with a Hewlett Packard Network Analyzer into a dipole antenna located just outside the magnet room, and leakage is measured by the headcoil using an RF Noise test sequence provide by the Service Menu. These tests show that the RF leakage around the door has not increased since the installation.

**A.2. RF Stability Tests:** The stability of the RF is one of the critical components needed for reliable MRI measurements, and for specialized applications (e.g., water suppression in spectroscopy measurements). Therefore, a procedure was developed for testing of the stability of the RF. The tests are conducted by inserting a small, un-tuned surface coil into the headcoil (Figure 1). The RF pulse transmitted by the headcoil is received by the surface coil, which is connected through an attenuator into the receiver path at the filter panel. Use of a special Service Menu sequence enables the attenuated RF pulse to be digitized by the receiver. Several thousand RF pulses are digitized and stored, and the maximum amplitude and phase variations, along with their standard deviations, are computed by an analysis program on the system. The tests showed less than 1% amplitude variation, and less than  $1^\circ$  phase variation, over approximately 5,000 RF pulses. This stability is considered adequate, but the tests will be repeated periodically to ensure that the stability does not degrade with time.



**Figure 1.** Test setup for the RF stability tests. The untuned surface coil (resting on the orange holder) is positioned within the TEM headcoil.

**A.3. Static Magnetic Field ( $B_0$ ) Stability Tests:** We tested  $B_0$  stability by measuring the water frequency of water phantom using the frequency adjust menu of the system. The water frequency was measured before and after running a gradient coil demanding echo planar imaging (EPI) pulse sequence for 10 min. The water frequency increased by 16 Hz from before to after the sequence. It remained stable at the higher frequency for the 5 min it was continuously observed. Running the EPI sequence for 10 min deteriorated the water line-width at half height from 13 Hz before to 18 Hz after the EPI sequence. These tests suggest that pulse sequences that put a high demand on gradient coil switching may induce small field drifts, presumably due to thermal heating. This small frequency shift may impact some applications, ie. spectroscopy and algorithms may have to be developed to correct for this effect. We also performed  $B_0$  frequency stability checks with the standard water phantom at different occasions. In the morning, when the system comes off standby mode, the water frequency fluctuates for about 5 min around  $\pm 3$  Hz. Within 25 min, the frequency fluctuations decrease to within  $\pm 1$  Hz. Thus, studies that depend on constant frequency should not be started until the system has warmed up for about 25 min.

**A.4. Shimming:** Automatic shimming of  $2 \times 2 \times 2$  cm<sup>3</sup> VOI in center of MRS phantom located in the isocenter of the magnet yields 4 – 5 Hz line widths after 2 iterations, off-center VOI yields 5 – 6 Hz line widths. Increasing the adjust volume to  $5 \times 5 \times 2$  cm<sup>3</sup> does not improve automatic shimming. Manual shimming of a  $2 \times 2 \times 2$  cm<sup>3</sup> VOI results in line widths as narrow as 2 Hz in the isocenter. In vivo shimming: Automatic shimming of  $2 \times 2 \times 2$  cm<sup>3</sup> VOIs in supratentorial cerebrum with 2 iterations generally yield line widths around 20 Hz, sufficient for baseline separation between Cho and Cr. Automatic shimming of a  $10 \times 10 \times 7$  cm<sup>3</sup> VOI for 3D STEAM SI in the cerebrum yields 30 Hz line width after 3 iterations, manual shim improves this to 27 Hz. Automatic shimming usually fails for hippocampus and cerebellum, because of excessive inhomogeneity in these brain regions. Manual shimming can improve homogeneity to

about 20Hz. However, manual shimming requires experienced operators to be performed reliably.

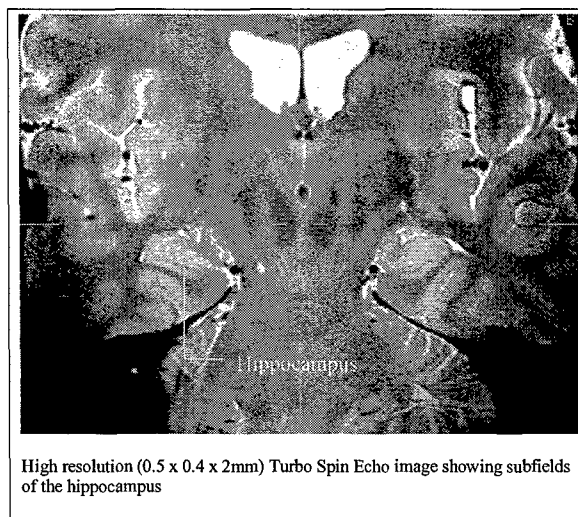
## **B. Brain Imaging**

**B.1. Very High Resolution Structural MRI:** There are relatively few whole body 4T MRI scanners installed worldwide. As a result, there is little work in the literature describing the optimal scanning techniques and imaging parameters for structural (anatomic) imaging at 4T. Our first task therefore was to determine a set of imaging sequences to use to acquire structural images of the whole brain at a resolution of 1mm x 1mm x 1mm. For  $T_1$ -weighted imaging, which provides high quality images with good contrast between gray and white matter, as well as suppression of cerebral spinal fluid (CSF), we compared the FLASH (Fast Low Angle SHot) and MPRAGE (Magnetization-Prepared Rapid Gradient Echo) sequences. After imaging a number of volunteers, we chose the MPRAGE sequence for its superior gray/white matter contrast. As there are a several parameters that can be manipulated to change the contrast in MPRAGE sequences, computer simulations were used to guide our choice of imaging parameters. We then optimized this set of parameters by imaging healthy volunteers on the 4T scanner. We also studied the acquisition of 3d (whole brain)  $T_2$ -weighted images, which provide a CSF mask and thus allow whole brain volume to be calculated. These images are also used in the automatic segmentation of gray and white matter. Because there is greater RF power deposition at 4T than at 1.5T (the field strength used for clinical imaging), we chose to use a variable flip angle imaging technique, which reduces power deposition, at the expense of slightly increased image blurring. In addition, we implemented a FLAIR (FLuid-Attenuated Inversion Recovery) version of this sequence that suppresses CSF and provides excellent contrast for white matter lesions.

Again, computer simulations were used to guide our choice of timing for this sequence. Our other structural imaging goal has been to find the optimal sequence to acquire high resolution (0.5mm x 0.5mm x 2mm) coronal images of the hippocampus, the structure in the brain that is used to form and retrieve memories (Figure 2). At the 4T, we have been able to acquire images that enable us to differentiate between different regions (known as subfields) of the hippocampus, something which has not been possible on our 1.5T scanner. Pathology studies and animal studies have found that certain diseases, such as Alzheimer's disease and Lewy Body dementia, as well as normal aging, affect different subfields of the hippocampus.

Therefore, we hope that the ability to identify subfields of the hippocampus at 4T will increase our power to differentiate between normal aging and disease processes such as Alzheimer's and other dementias.

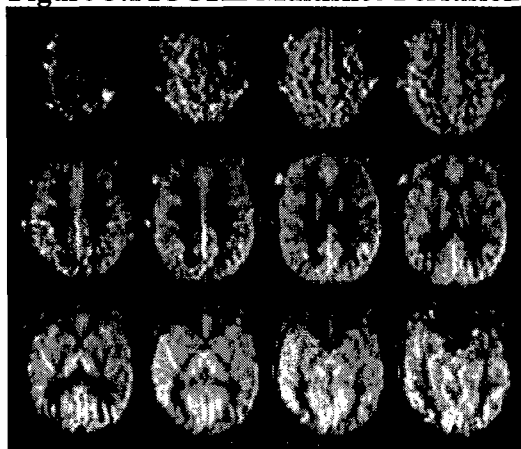
**B.2. Cerebral Blood Flow Measurements by Arterial Spin Labeling MRI:** Arterial Spin labeling (ASL) MRI uses endogenous blood water as tracer for cerebral blood flow. Since this method is entirely non-invasive and easy to perform during the same session than conventional MRI, it could become an attractive alternative to the current standards PET and



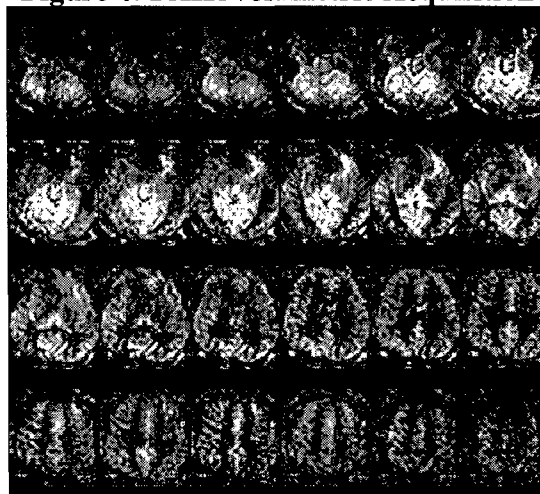
**Figure 2**

SPECT, which use radioactive tracers for measuring blood flow. We implemented and tested two pulsed ASL techniques on the 4T: a) PICORE, which is the proximal inversion of 100mm width using FOCI pulse. Total acquisition time=5min. (Figure 3); b) a volumetric technique based on FAIR, which is used in in-plane selective and non-selective inversion using hyperbolic secant pulse on a head coil. Total acquisition time=6min. (Figure 4). Perfusion images from both techniques are shown below. Both sequences yield sufficient signal to noise to measure blood flow. The FAIR volumetric acquisition provides seamless coverage of the brain with high efficiency. However, geometrical distortions at the lower regions in the brain are currently a major limitation for both ASL sequences. It is expected that geometrical distortions will be substantially reduced with parallel image acquisition, because less phase-encoding step are required and thus less distortions are introduced. In addition, gradient echo sequences can be replaced by spin-echo sequences to reduce geometrical distortions.

**Figure 3: PICORE Multislice Perfusion**

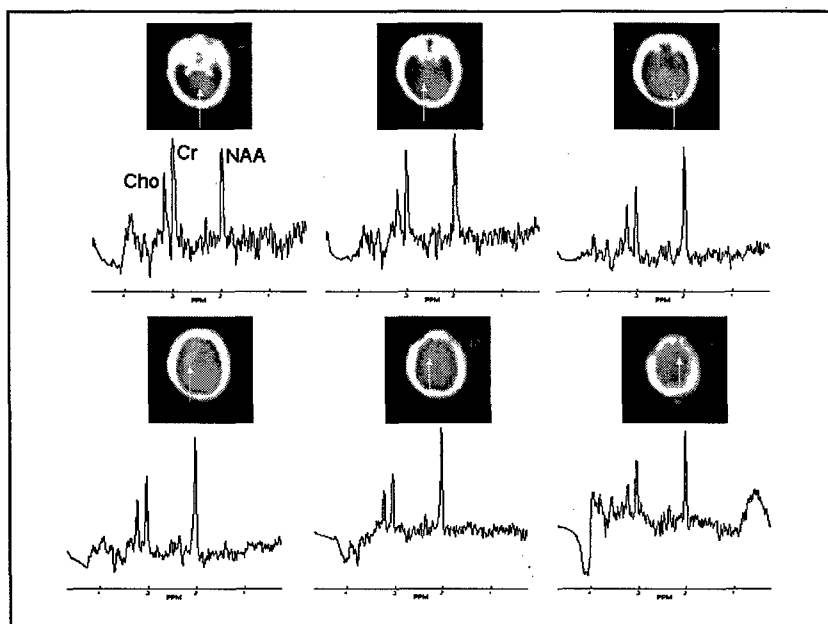


**Figure 4: FAIR volumetric Acquisition**



**B3: Volumetric Echoplanar Spectroscopic Imaging (EPSI):** A pulse sequence for volumetric echo-planar spectroscopic imaging (3D EPSI) was implemented on the 4 T system. Since this sequence had been designed originally for use on 1.5 T and 3 T systems, various adjustments had to be made to the pulse sequence as well as to the data processing software. The adjustments applied to the pulse sequence include changes to the design of the readout gradient, design of new adiabatic RF pulses to replace some of the existing RF pulses, and the addition of a second saturation pulse for outer volume suppression. These changes were implemented and tested in phantoms and healthy volunteers. The adjustments applied to the data processing software aimed at utilizing the increased spectral bandwidth available at 4 T. Several different approaches were tested on phantom data and the best performing algorithm was integrated into the data processing software. One example data set is shown below (Figure 5).

Figure 5



### KEY RESEARCH ACCOMPLISHMENTS

- The main research accomplishment over the past year was successful implementation of several key imaging techniques, especially high resolution structural MRI to study hippocampal subfields and volumetric arterial labeling perfusion MRI to measure brain function.
- In addition, we implemented imaging protocols for different projects, including studies of aging, dementia, and recovery from stroke.
- Since we have scanned only a small number of patients, there is not yet enough data to determine the power of MRI at 4T to detect neurodegenerative diseases.

### REPORTABLE OUTCOMES

1. We verified that the system works within the range of specifications.
2. We demonstrated that the expected gains in signal to noise and prolonged T1 relaxation provides images of superior quality compared to MRI at lower magnetic fields (ie. 1.5T)
3. Presentations:
  - a. Norbert Schuff, PhD: Regional Pattern of Hypoperfusion in Mild Cognitive Impairment and Alzheimer's disease by Arterial Spin Labeled MRI: presented at the Forum for Advanced Imaging Research (FAIR), Department of Radiology, University of California San Francisco, 2004.
  - b. Norbert Schuff, PhD: Non-Invasive Measurement of Brain Perfusion Using Arterial Spin Labeling MR; presented at the Research Seminars, DVA Medical Center San Francisco, 2004.

## CONCLUSIONS

The system performs within specification and improved sensitivity of MRI is obtained at 4T. The gain in sensitivity to detect neurodegenerative disorders needs to be determined by studying more patients and control subjects in the coming months and years. Our plans for the near future are to study more patients with Alzheimer's disease, Parkinson's disease, Depression, etc. to obtain pilot data for new grant applications. Furthermore we plan to improve perfusion, diffusion, and spectroscopy acquisitions and develop tools for processing the 4T MRI data. Last, we propose to use funds from this grant to support the following personnel: Derek Flenniken, Geon-Ho Jahng, Valerie Cardenas-Nicolson, Ashish Raj, David Ress, to be named Postdoctoral Fellow, and to be named Information Technologist. Mr. Flenniken will develop and implement software tools for transfer of 4T MRI data to offsite computer stations for further processing. Dr. Jahng will develop and refine arterial spin labeling perfusion imaging and diffusion imaging techniques at 4T. Dr. Cardenas-Nicolson will develop and refine image processing software for tissue segmentation, distortion corrections, and warping of 4T MRI data. Dr. Raj will develop improved parallel imaging techniques. Dr. Ress will implement high resolution imaging techniques. The to be named Postdoctoral Fellow will develop improved arterial spin labeling perfusion techniques. Last, the to be named Information Technologist will develop a reliable back-up system and database structure of 4T MRI data.