ABSTRACT

Aging, multiple sclerosis, stroke, trauma and tumor angiogenesis all involve some form of iron deposition. Iron has long been implicated in neurodegenerative disease, but only now are we able to monitor the changes in ferritin and hemosiderin *in vivo* with magnetic resonance imaging by using susceptibility weighted imaging (SWI). The mechanisms of these diseases remain largely unknown. Understanding the role iron plays as a biomarker of disease or as a participant in the chemical changes associated with the progression of disease is the goal of the iron-based research presented in this proposal. Based in part on the work from my lab, there has been an exciting breakthrough in the interpretation of increases in iron content in multiple sclerosis. My work has shown that there is a backward iron build up relative to the thalamostriate and medial venous drainage system. This suggests that there is a venous hypertension associated with iron build up that leads to endothelial breakdown. With this ammunition, it has now been shown by an Italian group led by Paolo Zamboni that my interpretation was correct and that multiple sclerosis patients have obstructions of the venous system in the neck and spine. He has successfully operated on more than 100 patients based on this hypothesis. Our immediate goal is to replicate his work in 100 patients using magnetic resonance imaging rather than ultrasound. We believe there may be many other manifestations of this venous disease. Therefore, in order to better understand the etiology behind aging, multiple sclerosis, stroke, trauma and tumor angiogenesis, we plan to create an international database for these diseases with a fixed neuroimaging protocol. This will allow us to map out the cerebral hemodynamics of both normals and patients and show how the vascular problems relate to the etiology of these diseases.

PROJECT NARRATIVE

We propose to investigate iron as a biomarker for the presence of vascular problems in multiple sclerosis, aging, stroke, cancer and traumatic brain injury. Using a new imaging technique referred to as susceptibility weighted imaging (SWI), we can map out not only changes in the venous vasculature but a build-up of abnormal iron deposition in the tissue. This should lead to an improved understanding of these debilitating diseases.

SCIENCE AREA: 03 – Clinical and Translational Research (HAACKE, EWART MARK)

ESSAY TITLE: Probing the etiology of neurological diseases using iron as a biomarker of vascular damage.

Project description: Damage to the vascular system may play a major role in a number of key neurological diseases than has heretofore been thought. As an example, consider the recent potential breakthrough in multiple sclerosis (MS) research presented in Bologna, Italy this year where it has been found that the etiology of MS may well be from stenoses in the jugular and azygous veins. The disrupted venous hemodynamics then leads to endothelial breakdown and the subsequent well known inflammatory demyelinating response. This out of the box thinking may have dramatic ramifications for not just MS but other diseases as well. This is what I have been promoting for the last few years. This proposal will highlight the need to rethink the role of both arterial and venous disease in aging and cancer for the former and MS, stroke and traumatic brain injury (TBI) for the latter. Therefore, my main focus is on the role of vascular damage in neurological diseases and the overarching hypothesis of this proposal is:

Hypothesis One: *"A major cause of diverse neurological diseases is vascular damage, the effects of which can be seen with magnetic resonance imaging (MRI)."*

Specifically, new methods, such as susceptibility weighted imaging (SWI), pioneered by myself, offer the ability to measure nanomoles of elements such as iron. The fact that iron binds to two major proteins (hemosiderin and ferritin) makes it detectable using MRI. We have recently shown that iron measured in the basal ganglia and thalamus most likely represents damage to the endothelium of the medial venous drainage system. If this proves to be correct, it will underlie what may be the real etiology of MS, a damaged venous system with a faulty hemodynamic response to the normal venous drainage. This then leads to damage to the endothelium, a breakdown of the vessel wall, iron and other biological effects penetrating the healthy tissue leading to inflammation and demyelination, the hallmarks of MS. Therefore, I propose a second hypothesis:

Hypothesis Two: *"Iron can serve as a surrogate marker for tissue damage, it can be seen in the form of ferritin and hemosiderin using SWI and will directly show the presence of vascular damage."*

During the past few years my group has been promoting the use of SWI in international multidisciplinary teams to try to tackle these complex neurological diseases. I am working to expand this multicenter collaboration using a fixed neurological imaging protocol to collect data from thousands to tens of thousands of cases in a format suitable for datamining. To date we have ten (10) sites around the world interested in working with us on the MS project alone. Once firmly established, it will be possible to expand their interests to other diseases. Based on these insights and concrete results, the three part goals of this work are: (i) to use iron as an endogenous contrast agent to image these diseases better; (ii) to use iron as a tool to drive basic research of these diseases into the micro-vascular realm; and (iii) to assist in the development of new drugs to protect and treat a damaged/deteriorating vascular system. This leads to the third hypothesis:

Hypothesis Three: *"Monitoring the early involvement of the microvascular system will make it possible to discover the etiology/pathogenesis of these diseases, to diagnose them more effectively at an earlier stage and hence to treat them more successfully."*

This direction of research truly meets the three criteria of the "Roadmap" initiative of: a) new pathways to discovery through novel approaches; b) developing team science; and c) enhancing clinical translational research through collaborative datamining. Although I presently have a deep understanding of the physics of imaging, and a more limited understanding of the anatomy and basic pathophysiology of disease, the successful study of these diseases will require me to grow into the broader areas of molecular imaging, animal studies and pathophysiology to test and prove/disprove the three hypotheses stated above. The work proposed herein could, and probably should, take up the major part of the next ten years of my research. What is exciting to me as an individual is that I have grown from the development of imaging technology and the study of anatomy to using imaging for functional studies and now to using imaging technology to study the pathophysiology of disease. I intend to expand my own knowledge base to the point where I can act most effectively and use my imagination and creativity to better address key questions like those posed in the three

hypotheses above, without the current restrictions associated with constantly attacking smaller problems to attain some constant degree of funding.

For 25 years my focus has been set on developing the technology for high resolution vascular and functional imaging of the central nervous and cardiovascular systems. Perhaps the most exciting development has been the realization that SWI and other imaging technologies now offer both a new source of imaging and the opportunity to probe the pathophysiology of disease. In human and animal studies, SWI makes it possible to perform molecular imaging without the need for an exogenous contrast agent. Instead, the *intrinsic iron* can serve as an *endogenous* marker, visualized by SWI, and therefore may serve as a surrogate marker for a variety of key disease processes. It has already been shown that SWI reveals 3 to 6 times more microbleeds, and can visualize diffuse axonal injury better than conventional imaging methods. Our collaboration with the Department of Neurosurgery at Loma Linda University in a longitudinal study of more than 100 elderly patients, 75 of them with mild cognitive impairment, already has shown that this may also be true in aging, Alzheimer's disease and dementia. That experience then suggested the need to look into other diseases like multiple sclerosis and tumors to see if there was any evidence for iron build-up or other indications of either perivascular disease or angiogenesis.

Formulating the concept and developing the insights into why macro and microvascular change may be a common thread to aging, multiple sclerosis, stroke, trauma and tumors:

Through a number of collaborating efforts already underway, I have been investigating dementia, MS and brain trauma patients and have discovered a remarkable similarity in the MR-visible manifestation of these diseases. Very recently, in the field of stroke imaging, it is now being recognized that white matter disease may be a result of vascular damage on the venous side. What is rather exciting is that much of the SWI data from patients with these diseases correlate well with histopathology findings obtained from stained cadaver brains. In the following material, I hope to draw attention to the fact that these seemingly unrelated diseases actually have a lot in common, enough to support the hypotheses stated at the beginning of this proposal. In the series of figures below, we paint a picture of the role of iron in assessing vascular disease.

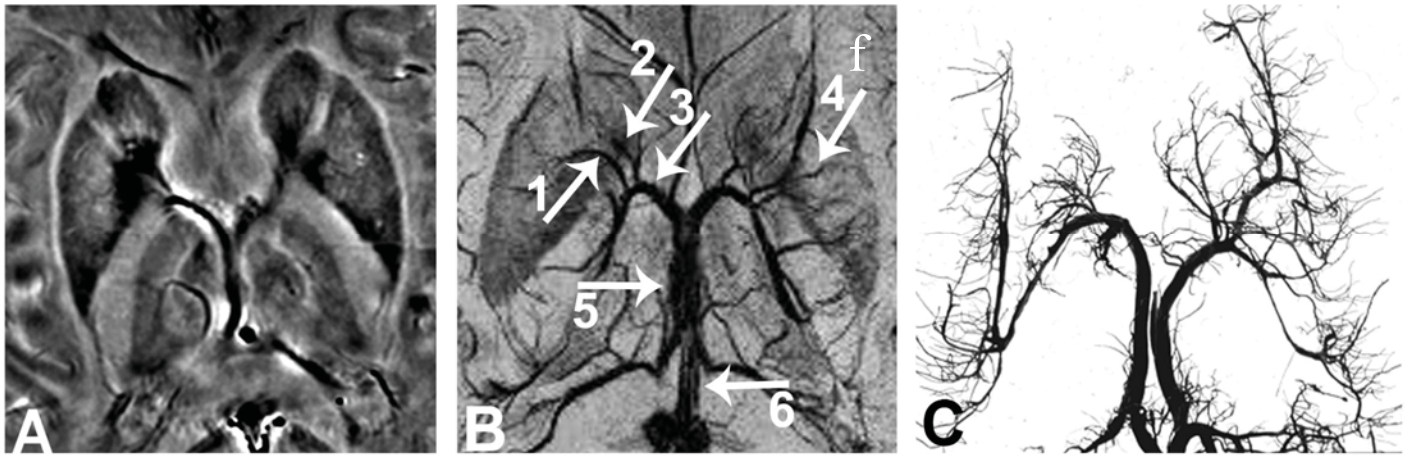

Figure 1: (A) SWI filtered phase showing increases in iron content in the basal ganglia directly related to the thalamostriate draining veins. (B) Minimum intensity projection SWI data showing the venous drainage system for the basal ganglia and thalamus. This includes: (1) the globus pallidus; (2) the caudate nucleus; (3) the thalamostriate vein; (4) the putamen; (5) the internal cerebral vein and (6) the vein of Galen. (C) A radiographic image of the veins from a cadaver brain study (courtesy of Georges Salamon).

This image, one of many we have now done in MS cases, reveals the anatomical relationship between iron deposition and damage to the thalamostriate venous system. We see the same effects in the mesencephalon and in the dentate nucleus. All these drain eventually into the straight sinus. Could there be general damage to the venous drainage system for MS patients? Prof. Paolo Zamboni (of Ferrara, Italy and the pioneer of the chronic cerebro-spinal venous insufficiency theory) believes that is the case. His group has shown that more than 80% of MS patients have stenotic jugular or azygous veins. We see iron as a breakdown product with SWI and we believe this may be iron in the affected endothelium of the vessel wall. There is in fact strong

pathophysiologic evidence from cadaver brain work demonstrating just this fact in venules in MS patients. We believe that our work in this direction will help change the face of research in MS. We will approach this work both from the perspective of animal and human epidemiological studies using imaging as our guide.

More recently, we have shown that the ring-like structures seen in MS (and which look very similar to the leuko-encephalopathy in cadaver brains) is also seen in oligodendrogliomas (probably representing leaky capillaries and the resulting hemosiderin). In both cases, if local microbleeding has taken place or if there is a large amount of monocyte activity, then any remnant hemosiderin would be picked up by SWI. It will be important to understand just what type of iron is being visualized and then be able to correlate this with the pathology that led to the presence of the iron in the first place. This can be done with a variety of techniques, such as atomic absorption spectroscopy, electron microscopy, or more recently with x-ray fluorescence spectroscopy (XRFS) at the Stanford Linear Accelerator. I visited this facility with faculty from the University of Saskatchewan in Canada last spring to see the results first hand and they are very impressive. XRFS can image other metals as well and currently has two unique detector types allowing either 50 μ resolution or 1 μ to 2 μ resolution. Once a general region of interest is found, one can zoom in on this area with higher resolution. For a variety of other experiments, we will need to separate ferritin from hemosiderin and ideally determine the states that different forms of iron are in and (for MRI in particular) whether these states are magnetic or not. As a former high energy physicist by training, this is all very rewarding to see these fields come together.

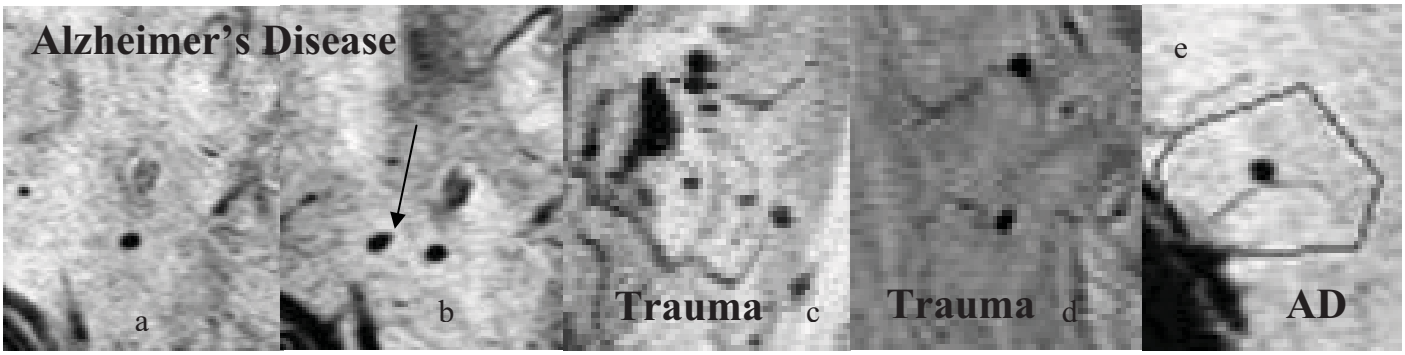

Figure 2: A series of SWI images from patients with dementia and trauma. (a) First image of a patient with mild cognitive impairment (MCI) showing one microbleed (MB). (b) A repeat study of the same patient who developed Alzheimer's disease (AD) one year later showing a new MB beside the first (black arrow). (c) A case of a motorcycle accident showing many MBs similar to the MCI case. Of 14 MCI patients, 6 showed MBs with SWI and all 6 developed AD. However, (d) is from the same trauma case as (c) showing similar small MBs. Finally, (e) shows bleeding near a sulcus and comes from one of the 6 cases with AD. Similar to the trauma case, this type of MB is seen in many of the AD lesions.

Figures 1 and 2 point to the broad implications of imaging iron. But it is not just imaging iron that we are after, it is using this new endogenous contrast agent as a biomarker for disease and even more important using it as a means to distill information related to the etiology of the diseases themselves. The fact that using iron has led us to an overarching hypothesis that microvascular damage plays a key role in many neurological and neurodegenerative diseases is a bonus. In fact, this research suggests that we need a broader focus in understanding the hemodynamics of the venous system in the human brain as well as the arterial system. This type of work does not yet exist but with the advent of high field systems and rapid imaging, it will now be possible to quantify the fluid dynamics in vessels using 4D (3D/1D) imaging methods.

These images tell a critical story. Let me summarize these points in four separate statements of what we have learned so far: *First, we can image iron at the nanomolar level and use it as an endogenous contrast agent. Second, iron correlates with a variety of vascular diseases. Third, iron may act as a marker for microvascular breakdown. Fourth, this new imaging biomarker may serve as a means to monitor a wide variety of neurovascular and neurodegenerative diseases (such as aging, MS, stroke, trauma and tumor angiogenesis) and to understand their etiology and lead to better treatment.*

The above hypotheses suggest that the specific aims of this research should: 1) validate the presence of vascular damage in the neurological diseases of interest; 2) validate the presence of iron in the form of either ferritin or hemosiderin and understand its role in the disease mechanisms; and 3) show that monitoring the

disease and the microvascular system (both anatomically and hemodynamically) can be used to better diagnose the disease and lead to better treatment of the disease. The medical payoff would be a dramatically improved diagnosis, improved understanding of the etiology and better treatment of theses diseases, and improved understanding of normal hemodynamics in the brain on both the arterial and venous sides. We want to better understand what damage is a precursor of disease rather than a result of the disease. Basically, can we differentiate cause from consequence? Our goal is to leapfrog beyond what we currently know about these diseases, better understand the etiology of the disease, better treat the disease and perhaps even prevent the onset of the disease. MS may serve as a prime example where all of these are imminently realizable.

The intriguing information discussed herein demonstrates that there are still substantive challenges remaining. These include proving whether the iron we see correlates with either ferritin or hemosiderin and what role these play in the biochemistry of the individual disease. The richness of the physics of MRI along with proper histopathological evaluations will likely help to provide the answers. Furthermore, a number of key questions can be extracted from recent reviews on aging, cerebrovascular disease, stroke and the role of iron in neurodegenerative diseases. The issues that remain to be studied during the next five years include: how perfusion loss results from vascular damage and leads to a cascading effect of neuronal and further vascular damage; how damage to the locus coeruleus can lead to a breakdown in noradregenic innervation of vessels; correlating iron increase and microbleeds with stiffer and thicker vessel walls more prone to inflammation; validating that the loss of pericytes may lead to transient blood-brain-barrier breakdown; using new contrast agents sensitive to iron content for the detection of macrophage activity in diseases such as multiple sclerosis; taking advantage of molecular imaging techniques to validate some of the above hypotheses; investigating how well diabetes and hypertension can be assessed with this new approach; studying how much of dementia is due to “cognitive stroke”; investigating what special hemodynamics and fluid dynamics can be invoked to strengthen cerebral blood flow; showing that trauma is a risk factor for dementia; probing how ferritin and hemosiderin are associated with angiogenesis and perivascular disease in MS; showing how faulty hemodynamics leads to endothelial damage and hemosiderin in the vessel wall; and showing that damage of the venous system causes decreased perfusion in addition to all other known arterial risk factors (including the atherosclerosis that causes hypoperfusion). If I were to receive this award, I would be able to begin addressing many of these critical questions in a coherent and productive fashion.

To unravel these questions involves a two-fold approach of imaging humans and animals. The animal studies will be performed to address issues of quantification, study disease progression through molecular imaging and validae many of the assumptions related to microbleeds, oxygenation loss, iron build-up and the form of the iron itself, whether ferritin or hemosiderin. We will design new animal models to address the effects of reduced flow through major veins for example or changes in perfusion. The human studies will be performed on normal age-matched volunteers and a cohort of patients in aging, multiple sclerosis, trauma and tumors.

Evidence of innovative work: My research in the last 25 years has led to a number of key developments in imaging, specifically the invention of MR angiography, the development of fast imaging and the invention of susceptibility weighted imaging. My diverse interests include clinical translational research in aging, multiple sclerosis, cancer aligned with imaging research in MR technical development, image processing and image reconstruction. The marriage of these fields has produced methods which are viewed internationally as major advances in the field. Since coming to Detroit as head of the MR research program, I have built up both a broad spectrum of local collaborators having been involved in more than 50 projects and have established an international network of faculty to tackle these problems on a large number of clinical patients. Combining this intellectual approach with my enthusiasm and energy levels in research with nearly 200 publications and several books, it should be clear that whatever team I put together we will make breakthroughs in the next five years. My strategies have always been to integrate basic science with clinical translational research; these two directions feed off each other and lead to major new developments.

How the planned research differs from my past or current work: This work will finally give me a chance to forge a coherent group with expertise in a variety of fields including anatomy, pathology, physiology, neurology and radiology to attack the above mentioned problems. Furthermore, an attempt will be made to draw together multiple sites around the world to use a fixed imaging protocol and to create an international team science approach. The early foundations for this network of collaborators has already begun for the MS project.

Suitability for Pioneer Award Program: The proposed broad based approach to attack these problems is uniquely suited to the pioneer award. It would not be expected to receive conventional R01 funding as it would be viewed as tackling too many diverse problems. But that is exactly what is needed, an integrated approach to neurological problems with the promise to change future diagnosis and treatment for the disease.

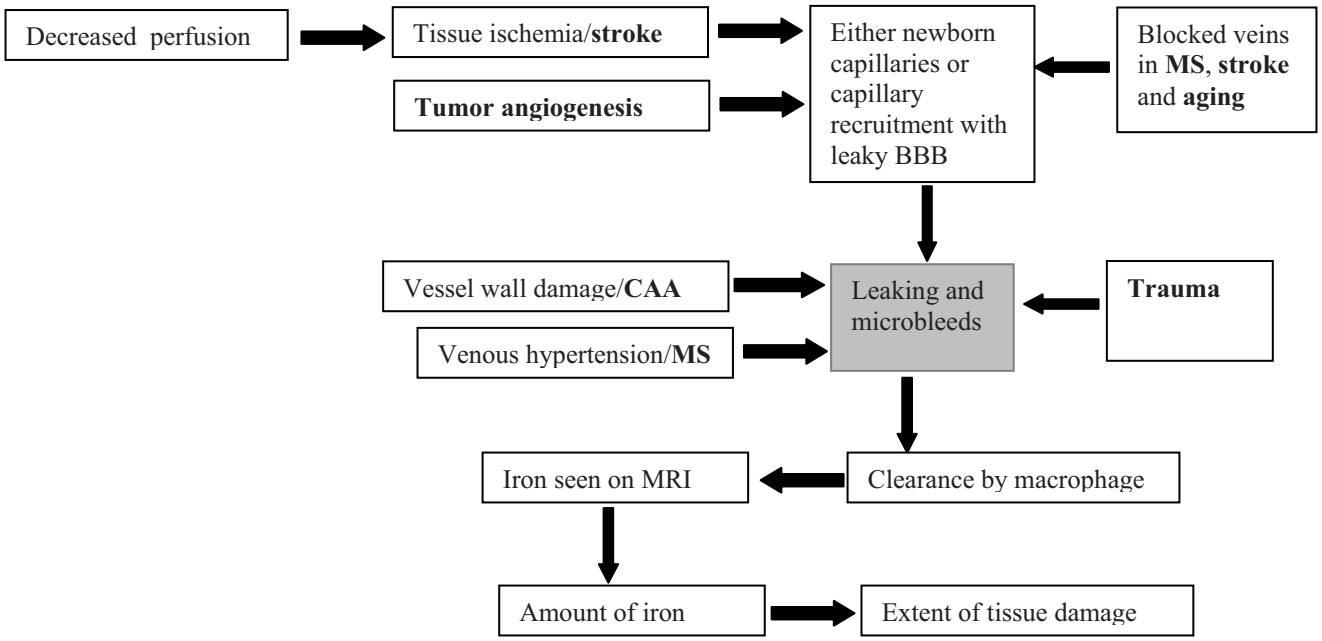

Figure 4: *Iron as a surrogate marker for vascular disease: following progression of the disease and probing the etiology:* This schematic is used to show the pathway for a given problem that leads eventually to the leaking and microbleeding we have shown for aging, multiple sclerosis, stroke, trauma and tumor imaging. All these diseases meet in the shaded area. Our preliminary results also converge on the shaded area, although we have some evidence for some of the earlier stages in these diseases (see elements above the shaded box) through their iron content as seen using magnetic resonance imaging. We want to exploit the *in vivo* imaging techniques available with high field MRI as well as a variety of other pathophysiological methods to investigate the earlier stages of these diseases, monitor the progression of the disease and, if treatments are available (as in multiple sclerosis), monitor the treatment of the disease.

Summary: This project will build on recent advances in neurovascular imaging to identify common iron-related and iron-mediated degenerative processes that are thought to underlie a wide variety of neurovascular diseases. The findings have the potential to transform diagnostic and therapeutic approaches for stroke, vascular dementia, multiple sclerosis, brain trauma and brain tumors. The innovation we provide comes from insights gained through my strong physics and imaging background and my ability to propose new approaches that cut across many fields from physics to physiology. The new paradigm I propose is that damage to venous drainage is a key element in the pathogenesis of many diseases, one that has heretofore been overlooked. By using new MR technology developed by my group in combination with an integrated approach from many other fields to address the issues of flow hemodynamics and vessel wall damage, we may be able to break into an entirely new domain of mapping out the etiology of a number of these diseases. I have been persistent in my approach of integrating new physics into the MR community and it has paid off with these new discoveries. During the last 5 years, I have precociously begun building a strong set of collaborations. My work is attracting major interest in the field, especially at clinical sites that would like to be involved. Focusing now on physiology, anatomy, new imaging approaches, and large scale population studies is a new thrust for my usual imaging physics-oriented research endeavors. The scope of what I propose here would not easily fit into the usual R01 venue as there may appear to be too many components, too many people and too many as of yet unproven hypotheses. However, by bringing together the necessary expertise via a national collaborative effort consisting of pathologists, physiologists, biochemists, neuroradiologists and imaging experts, I can envision a very successful and most important contribution to society. Finally, it is my belief that we need this new paradigm approach in medical research today that takes advantage of imaging data from around the world and as evidenced by what is happening in MS, thanks in part to the work we have carried out using SWI, this approach is already beginning to bear fruit. We need to head in this direction.

MOST SIGNIFICANT RESEARCH ACCOMPLISHMENT

Understanding the role of field effects in magnetic resonance imaging and its implications to clinical diagnosis and treatment of patients.

Perhaps the most significant research accomplishment that I have made in the past ten years is probing the role of magnetic field variations in the human body and applying the results to clinical translational research. This work, which began more in the theoretical domain, had immediate clinical applications, and through the development of susceptibility weighted imaging (SWI) now offers better diagnosis and treatment of disease. SWI may in fact become an important biomarker not just for different forms of iron but in investigating the etiology of a number of key diseases such as aging, multiple sclerosis, stroke and trauma. The method that I developed is now available worldwide thanks to its adoption by at least one major vendor and it is under consideration by other major vendors as well. It is becoming part of a standard neuroimaging protocol eventually to be run on all neuroimaging cases. This technique is so powerful that it may have far reaching implications in the study of breast cancer, atherosclerosis and cardiovascular imaging (to name a few). Further, SWI may help drive research in other fields such as pathology, neurology and neuroscience. Throughout these years I have also trained many people in MRI (more than 50) who have now become senior faculty and run their own research laboratories.

This work began by looking at the role that field inhomogeneities played in dephasing moving spins. That led the seminal paper on motion compensation in 1987 (AJR, 48, 1251). Not long after this, I began evaluating the role of high resolution to define how signal dephasing was manifest in 3D gradient echo imaging and from this published a precocious paper on this topic in 1989 (Radiology, 70, 457) and again ten years later as a review of these concepts in 1997 (JMRI, 7, 266). This fundamental underpinning made it possible to understand how to not only remove T2* effects but also collect MR spectroscopic data without a concern for T2* loss at all using chemical shift imaging. Further development of this T2* theory led to the seminal paper on static field dephasing published in 1994 (MRM, 32, 749). At that point, I realized that one could perform single voxel spectroscopy or resting state blood oxygenation level dependent (BOLD) imaging using phase information. This work published in 1997 (Radiology, 204, 272) led me to focus on the local susceptibility effects from biomarkers such as blood oxygenation, iron and calcium to name a few. This high resolution 3D technique was immediately recognized as a means to image veins even when there was no flow present because of the local deoxyhemoglobin content. Further work into enhancing contrast, processing schemes and partial volume effects then led to the seminal paper on “Susceptibility Weighted Imaging” or SWI published in 2004 (MRM, 52, 612). In this paper, we proposed using the phase information for a number of key new imaging directions from measuring iron to suppressing fat in coronary artery imaging. More recently, we have spent four years researching iron in aging using the SWI filtered phase information to monitor iron throughout the brain 2007 (JMRI, 26, 256). SWI has also proven to be a new window into imaging microhemorrhages which may prove to be a marker for up to 35% of dementia or Alzheimer’s cases. Finally, an understanding of these field phenomena is now attracting attention in the form of “Susceptibility Mapping” or SM. This technique promises to be the next extension of SWI that can serve as a quantitative probe of local tissue magnetic field effects, bringing us full circle. SM may allow us to quantify oxygen saturation, measure the amount of ferritin and hemosiderin or iron-based contrast agents bringing us as close as possible to molecular imaging in living beings without requiring a biopsy. Having a strong background in basic science has led me to the development of new ideas and an improved understanding of the imaging and its clinical applications. For this work, my educational accomplishments and my fundamental research in MRI, I won the 2004 Gold Medal of the International Society for Magnetic Resonance in Medicine in Kyoto.

SWI has since blossomed into a powerful new approach in magnetic resonance imaging being used by researchers and clinicians around the world. It has been one of the keys that has helped unlock the etiology of multiple sclerosis (JMRI 29, 537, 2009). The marriage of my background in magnetic resonance angiography and magnetic field effects and the many years of applying these techniques to neurovascular disease has led to the realization that many diseases may have a neurovascular disease component to their etiology. This may in fact be in the form of hemosiderin which creates a local field effect both microscopically and macroscopically. *Therefore, one might say it is the clinical translational research on the study of the brain’s vasculature and neurological diseases using susceptibility weighted imaging that is my most significant and far reaching contribution to society.*

PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research meets the definition of 'Clinical Research'. The following represents an example of only one of the potentially many projects that are involved in this proposal. The same may hold true not just for multiple sclerosis but also for aging, stroke, trauma and brain tumors. Inclusion and exclusion criteria will change depending on the project.

Human Subjects Involvement and Characteristics

At least 100 MS patients will enter this study over a two (2) year period. Patients will be recruited from many sites around the world including the United States of America, China, Japan, Canada, Germany and any others willing to participate in this open study.

To date, the sites involved are:

USA Detroit Medical Center (DMC), Detroit, MI
Michigan State University (MSU), East Lansing, MI

China Xuan Wu Hospital, Beijing
Union Hospital, Wuhan

Japan Hokkaido University, Sapporo
Iwate Medical University, Morioka

Canada Hamilton General Hospital at McMaster University, Hamilton
Saskatoon City Hospital at Saskatoon University, Saskatoon
University of Alberta, Edmonton, Alberta

Germany Friedrich-Schiller University, Jena

Brain MRI scans will be obtained two (2) times in this study: the first time at entry and one year later. The numbers of patients in the different disease categories is based on the approximate prevalence of the clinical subtypes of MS (see http://www.nationalmssociety.org/about-multiple-sclerosis/what-is-ms/index.aspx). All MS patients will be enrolled in the first year. The second year will be used for follow-up studies and data analysis.

Specific inclusion and exclusion criteria are as follows:

Inclusion Criteria:

- Patients who suffer from clinically definite MS for at least two (2) years with a RR, SP or PP disease phenotype.
- Patients who suffered from CIS suggestive of MS with the first clinical attack in the preceding 3 months and at least four focal abnormalities on T2WI.
- Aged from 20-59 years old.
- Eligibility for MRI per routine screening checklist.

Exclusion Criteria:

- History of other major illness, a prior known neurological disorder other than MS or substances abuse.
- Known contraindication to MRI such as pacemaker, pregnancy, other non-MR compatible implanted device.
- Patients with moderate to severe kidney disease that have impaired ability to filter the contrast agents.

Sources of Materials

Two (2) types of data will be obtained in the study: imaging data and neurological assessment. Clinical coordinators will screen and refer MS patients to MRI scan. Brain MRI scans will be obtained twice in this study. Each time an MRI is performed, patients will be assessed neurologically by a single physician who is unaware of the MRI results in the same week. Disability will be measured using the Expanded Disability Status Scale (EDSS). An ambulation index test will be done, which is basically just measuring how fast the person can walk 25 feet. At follow-up evaluations, patients will be considered worsened if they have an EDSS score increase ≥ 1.0 when the baseline EDSS is < 6.0, or an EDSS increase ≥ 0.5 when the baseline EDSS is ≥ 6.0. EDSS changes will always be confirmed by a second visit after a month, relapse-free interval. During the study, the occurrence of clinical MS relapses will be recorded. Axial 3D T1WI, 2D T2WI, 2D FLAIR, FLOW quantification sequences, SWI, dynamic MRV Vertex to thoracic inlet, and post-contrast axial 3D T1WI will be included in each scan.

Potential Risks

The potential risks in this study are minimal. The primary risk associated with neurological testing will be anxiety or frustration during the testing procedures. The imaging procedure has no increased risk beyond that of a regular MRI scan. Hazards associated with MRI are poor screening procedures and accidental metallic projectiles. Some participants might experience some mild discomfort from loud noises and confined space associated with the MR scanner. During scanning, participants may or may not experience warming of the skin due to energy absorption from radio waves used in MRI.

In addition to specific risks associated with MRI the following minimal risks are associated with injecting a contrast agent into a vein: Slight pain, bruising, bleeding or infection at the site where the intravenous catheter is placed. Occasionally, nausea, lightheadedness or fainting may occur.

Potential side effects related to the contrast agent (gadopentetate dimeglumine) are:

Headache 4.8% the majority of which are mild, nausea 2.7%, coldness at injection site 2.3%, dizziness 1%. Serious allergic reaction is less than 1%, which may include itching, rash, hives, facial swelling and difficulty breathing.

Adequacy of Protection against Risks

Subjects with moderate to severe renal insufficiency are at increased risk to develop nephrogenic systemic fibrosis with the administration of gadolinium based contrast agents and have been excluded from this study.

Patient Recruitment/Retention and Informed Consent

Recruitment: Participants will be provided with a consent form that they submit to the investigator prior to the commencement of the study. The consent form contains information and an outline of what study entails. Each subject will fill out a questionnaire to assess his or her MRI compatibility. The investigator will inform patients that the information given in the screening questionnaire will be held confidential between the participant and the investigator to minimize social risks associated with lost of confidentiality. Before MRI examination, the investigator will orally describe the study and procedures involved and answers any questions asked by a potential participant. They will be informed that they can terminate the study at any point in time without any prejudice from the investigator's side. If the participant decided to withdraw at any time during or after the study, the investigator will ask if they would like to discuss any matters or concerns. The investigator will give a full and objective explanation about this study and answer their questions. The decision of participants will be respected and the data collected during the experiment of these patients will not be used in the study.

Protection against Risk

MRI safety: All participants will be thoroughly screened before entering the MR suite. Each subject will fill out a questionnaire to assess his or her MRI compatibility. Head position will be standardized and a cloth and/or sponge will be used to minimize head movement and also make the subject comfortable. Each subject will be provided with ear plugs to minimize the noise. The scan team and subject will be able to communicate via an intercom system during the exam. An emergency "panic" bulb will be provided, which when pressed by the subject will notify the MRI technologist in the control room to stop the scan immediately, and if necessary remove the subject from the scanner. A window in the control room allows the investigator and scan team to monitor the participant for distress at all times. Regarding skin warming, the power output of the system is monitored by a computer and does not allow scanning to continue if the limits approved by FDA of 3.2 W/kg are exceeded. Patients will not be scanned if they are medically unstable.

Pharmacologic MRI safety: The scans requiring an injection of a contrast agent will be carried out in the present of a nurse or physician experienced in MRI contrast reactions. Subjects with a known allergy to MRI contrast agents will not be given contrast.

Data Monitoring: The imaging data will be saved in DICOM format on a CD. Processed data will be reloaded back to the data server for easy sharing between investigators. Patients will be assigned a sequential case number that is not based on any unique patient-identifiable data. Header information will be stripped prior to be saved in a CD. Demographic information and results of clinical assessment will be obtained from medical records with consent. Confidentiality will be respected and no information that discloses the identity of the subject will be released or published without consent unless required by law.

Potential Benefits of the Proposed Research to the Subjects and the scientific community or society

MS patients may benefit from the enhanced neuroimaging performed in this study because of the new MR technique we will use. The potential benefit to society may be to establish a new biomarker (iron) for MS to better monitor and prognosis MS as well as providing a new aspect for MS patients' treatment by curing the cause of MS pathology if our hypotheses were proven to be true.

PROTECTION OF VERTEBRATE ANIMALS

These studies will likely be carried out on rats and plan to develop models that affect the flow to the brain. One such model for multiple sclerosis (MS) might be creating a venous stenosis in one or both jugulars and possibly in a major vessel in the spine. This flow obstruction is then expected to lead to vessel wall damage and neurovascular effects similar to those seen in MS. These animals will be scanned with conventional methods, susceptibility weighted imaging (SWI), magnetic resonance angiography (MRA) and flow quantification (FQ) to demonstrate the disease is magnetic resonance (MR) visible and that the damage corresponds to the progression of the disease. The anesthesia, impact and MRI studies will be performed at 7T on a Bruker CLINSCAN unit with a Siemens interface. The scanner is part of the MRI Research Center at Wayne State University (WSU).

All the rats will be kept in a controlled environment in the Departmental of Laboratory Animal vivarium facilities at the WSU School of Medicine. The average temperature of these facilities is approximately 22 degrees Celsius and 30-70% relative humidity. The vivarium is equipped with a ventilation system which provides 12 air changes per hour. Additionally, husbandry practices, such as bedding-change and cage washing frequency, will be employed to ensure the well-being of the animals. Light will be supplied on a 12 hr on, 12 hr off cycle.

If pain, distress, infection, or severe debilitation is evident, animals will be euthanized. As is consistent with the Panel on Euthanasia of the American Veterinary Medical Association, the rat will be euthanized by lethal dose of carbon dioxide or halothane or (sodium pentobarbital (120mg/kg). This method of euthanasia is not painful and minimizes any discomfort experienced by the animal.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. * First Name: Ewart Middle Name: Mark

* Last Name: Haacke Suffix:

Position/Title: Director Department:

Organization Name: The MRI Institute for Biomedical Research Division:

* Street1: 440 East Ferry Street

Street2:

* City: Detroit County: Wayne

* State: MI: Michigan Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 48202

* Phone Number: 313-758-0065 Fax Number: 313-758-0068

* E-Mail: nmrimaging@aol.com

Credential, e.g., agency login: ak5444

*** Project Role:** PD/PI **Other Project Role Category:**

***Attach Biographical Sketch** HAACKE_BIOSKETCH_2009.pdf Add Attachment Delete Attachment View Attachment

Attach Current & Pending Support CURRENT_AND_PENDING_SUPPORT.p Add Attachment Delete Attachment View Attachment

PROFILE - Senior/Key Person 1

Prefix: * First Name: Middle Name:

* Last Name: Suffix:

Position/Title: Department:

Organization Name: Division:

* Street1:

Street2:

* City: County:

* State: Province:

* Country: USA: UNITED STATES * Zip / Postal Code:

* Phone Number: Fax Number:

* E-Mail:

Credential, e.g., agency login:

*** Project Role:** **Other Project Role Category:**

***Attach Biographical Sketch** Add Attachment Delete Attachment View Attachment

Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

OMB Number: 4040-0001
Expiration Date: 04/30/2008

ADDITIONAL SENIOR/KEY PERSON PROFILE(S)		Add Attachment	Delete Attachment	View Attachment
Additional Biographical Sketch(es) (Senior/Key Person)		Add Attachment	Delete Attachment	View Attachment
Additional Current and Pending Support(s)		Add Attachment	Delete Attachment	View Attachment

OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
E. Mark Haacke, PhD	Director
eRA COMMONS USER NAME ak5444	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Toronto	B.S.	1973	Mathematics & Physics
University of Toronto	M.S.	1975	Theoretical Physics
University of Toronto	Ph.D.	1978	High Energy Physics

A. Positions and Honors.

Positions and Employment

1981-1983 **Research Geophysicist**, Gulf Research and Development, Pittsburgh, PA.
1983-1985 **Senior Research Scientist**, Picker International, Highland Heights, OH.
1985-1989 **Assistant Professor of Radiology and Physics**, Head, MR Physics and Basic Science. Case Western Reserve University, Cleveland, OH.
1989-1993 **Associate Professor**, Department of Radiology with appointments in Physics and Biomedical Engineering, Case Western Reserve University, Cleveland, OH.
1993-1999 **Professor of Radiology**, Director MR Imaging Research, Mallinckrodt Institute of Radiology, Washington University, St. Louis, MO.
1999-Present **Director**, The MRI Institute for Biomedical Research, Detroit, MI.
2002-Present **Professor of Radiology**, Wayne State University, Detroit, MI.
2002-Present **Director**, Harper University Hospital, Magnetic Resonance Imaging Facility, Detroit, MI.
2002-Present **Professor of Biomedical Engineering**, Wayne State University, Detroit, MI.
2002-Present **Adjunct Professor**, Loma Linda University, Loma Linda, CA.
2005-Present **Adjunct Professor**, Department of Electrical and Computer Engineering at McMaster University and the Brain-Body Institute at St Joseph's Healthcare in Hamilton, Ontario, Canada.

Other Experience and Professional Memberships

1983-1985 **Lecturer in Physics**, New course on MRI, Case Western Reserve University, Cleveland, OH.
1992-1992 **Associate Editor**, IEEE for Transactions on Medical Physics.
1992-1994 **Chairman**, Liaison Committee at the Society for Magnetic Resonance Imaging (SMRI).
1992-1994 **Co-founder**, Joint Merger Evaluation Committee for the Society for Magnetic Resonance Imaging (SMRI) / International Society for Magnetic Resonance in Medicine (ISMRM).
1993 **Vice-President**, Interim Board at the Society of Magnetic Resonance Imaging (SMRI).
1993-1994 **President**, Society of Magnetic Resonance Imaging (SMRI).
2007-Present **Assoc Chair**, School of Medicine, Dept of Biomedical Eng, Wayne State University, Detroit, MI.

Honors (Since 2000)

2000 Poster Prize of the XXVI Congress of the European Society of Neuroradiology 2000. J.R. Reichenbach, L. Jonetz-Mentzel, C. Fitzek, H.-J. Mentzel, E.M. Haacke, W.A. Kaiser.
2002 Scientific Exhibition Award ECR 2002 Cum Laude. J.R. Reichenbach, C. Fitzek, L. Jonetz-Mentzel, D. Sauner, H.-J. Mentzel, E.M. Haacke, W.A. Kaiser. European Congress of Radiology
2004 Gold Medal Award, International Society of Magnetic Resonance in Medicine
2006 Wayne State University, Office of the Vice President for Research, Research Mentors Award Program for New Faculty for mentoring of Dr. Yu-Chung Norman Cheng
2006 RSNA Educational Exhibit Award LL-NR4709 entitled "Susceptibility Weighted Imaging (SWI) of the Brain: Pictorial Review of the Technique, Anatomy, and Pathology" T. Hirai, MD, Kumamoto JAPAN; M. Akter; M. Kitajima, MD; T. Okuda, MD; E.M. Haacke, PhD; Y. Yamashita, MD

2008 Best Abstract Award “Improving the detection of diffue axonal injury by complementary use of advanced MRI" at the 6th North American Brain Injury (NABIS) Annual Conference. Z. Kou, R. Benson, R. Gattu, M. Haacke. The abstract presented our breakthrough on a complementary use of SWI and DTI techniques for injury detection.

2009 Regional Scholarship for Asia “Imaging the Vessel Wall in Major Peripheral Arteries using Susceptibility Weighted Imaging: Visualizing Calcifications” at the 12th Annual Society of Cardiovascular Magnetic Resonance (SCMR). Qi Yang, Kuncheng Li, Jiangtao Liu, S. Barnes, Z. Wu, J. Neelavalli, J. Hu, E.M. Haacke.

B. Selected peer-reviewed publications. (Since 2008, selected from a total of 204 peer-reviewed publications)

1. J. Li, J.P. McAllister II, Y. Shen, M.E. Wagshul, J.M. Miller, M.R. Egnor, M.G. Johnston, E.M. Haacke, and M.L. Walker. Communicating Hydrocephalus in Adult Rats with Obstruction of the Basal Cisterns or the Cortical Subarachnoid Space. Experimental Neurology 2008 – 211:351-361.
2. J. Hu, Y. Yu, C. Juhasz, Z. Kou, Y. Xuan, Z. Latif, K. Kudo, H.T. Chugani, E.M. Haacke. MR Susceptibility Weighted Imaging (SWI) Complements Conventional Contrast Enhanced T1 Weighted MRI in Characterizing Brain Abnormalities of Sturge-Weber Syndrome. JMRI 2008 – 28:300-307.
3. C.E.A.Batista, H.T. Chugani, J.Hu, E.M. Haacke, M.E. Behen, E.J. Helder, C. Juhasz. Magnetic Resonance Spectroscopic Imaging Detects Abnormalities in Normal-Appearing Frontal Lobe of Patients With Sturge-Weber Syndrome. J Neuroimaging 2008 - 18:306-313.
4. Y. Shen, Y-C. N. Cheng, G. Lawes, J. Neelavalli, C. Sudakar, R. Tackett, H.P. Ramnath, E.M. Haacke. Quantifying magnetic nanoparticles in non-steady flow by MRI. MR Mater Phy 2008 - 21:345–356.
5. D.S. Pandian, C. Ciulla, E.M. Haacke, J. Jiang, M. Ayaz. Complex threshold method for identifying pixels that contain predominantly noise in magnetic resonance images. JMRI 2008 - 28:727-735.
6. E. M Haacke, S. Mittal, Z. Wu, J. Neelavalli, Y.C. Cheng. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR 2009 - 30:19-30.
7. Z. Wu, S. Mittal, K. Kish, Y. Yu, J. Hu, E.M. Haacke. Identification of calcification with MRI using susceptibility-weighted imaging: a case study. JMRI 2009 - 29:177-182.
8. B.G. Sood, Y. Shen, Z. Latif, X. Chen, J. Sharp, J. Neelavalli, A. Joshi, T.L. Slovis, E.M. Haacke. Aerosol Delivery in Ventilated Newborn Pigs: An MRI Evaluation. Pediatr Res. 2008 – 64:159-164.
9. Y. Xu and E.M. Haacke. An iterative reconstruction technique for geometric distortion-corrected segmented echo-planar imaging. MRI 2008 - 26:1406-1414.
10. Rowe, D.B., Haacke, E.M.: Thresholding Complex Magnetic Resonance Images Using Magnitude and Phase. Proc. Am. Stat. Assoc., Biometrics Section – 2008;13:1922-1929.
11. Z. Wu, S. Mittal, K. Kish, Y. Yu, J. Hu, E.M. Haacke. Identification of Calcification with MRI Using Susceptibility-Weighted Imaging: A Case Study. JMRI 2009 – 29:177-182.
12. Y.C. Cheng, J. Neelavalli, E.M. Haacke. Limitations of calculating field distributions and magnetic susceptibilities in MRI using a Fourier based method. Phys Med Biol. 2009 - 54:1169-1189.
13. S. Mittal, Z. Wu, J. Neelavalli, E.M. Haacke. Susceptibility-Weighted Imaging: Technical Aspects and Clinical Applications, Part 2. AJNR 2009 – 30:232-252.
14. E.M. Haacke, M. Makki, Y. Ge, M. Maheshwari, V. Sehgal, J. Hu, M. Selvan, Z. Wu, Z. Latif, Y. Xuan, O. Khan, J. Garbern. Characterizing Iron Deposition in Multiple Sclerosis Lesions Using Susceptibility Weighted Imaging. JMRI 2009 – 29;537-544.
15. S.R.S. Barnes and E.M. Haacke. Susceptibility Weighted Imaging: Clinical Angiographic Applications. MRI Clinical N Am 2009 - 17;47-61.
16. J. Neelavalli, Y-C.N. Cheng, J. Jiang, E.M. Haacke. Removing Background Phase Variations in Susceptibility Weighted Imaging Using a Fast, Forward-Field Calculation. JMRI 2009 – 29;937-948.
17. Y. Ge, V.M. Zohrabian, E-O. Osa, et al. Diminished visibility of cerebral venous vasculature in multiple sclerosis by susceptibility-weighted imaging at 3.0 T. JMRI 2009 – 29;1190-1194.
18. E.S. Manova, C.A. Habib, A.S. Boikov, M. Ayaz, A. Khan, W.M. Kirsch, D.K. Kido, E.M. Haacke. Characterizing the mesencephalon using susceptibility weighted imaging. AJNR 2009 - 30;569 –574.
19. Q. Yang, J. Liu, S.R.S. Barnes, Z. Wu, et al. Imaging the Vessel Wall in Major Peripheral Arteries using Susceptibility Weighted Imaging: Visualizing Calcifications. JMRI 2009 - 30;357-365.
20. Hillman GG, Singh-Gupta V, Zhang H, Al-Bashir AK, Katkuri Y, Li M, Yunker CK, Patel A, Abrams J, Haacke EM. DCE-MRI of vascular changes induced by sunitinib in papillary renal cell carcinoma xenograft tumors. Neoplasia 2009 - 11;910-920.

CURRENT AND PENDING SUPPORT – HAACKE, EWART MARK (PI)

Current:

R01 NS048349 (Quan) 12/01/2004 – 11/30/2009 0.60 calendar
National Institutes of Health $100,000 (sub only)
In Vivo MR Evaluation of Cell Therapy for Stroke
The major goals of this project are to demonstrate that MR tracking magnetic labeled cells is a valid new technique for studying cell therapy for stroke, which will lead to optimization of cell transplantation protocols and improved management of stroke.

Contract Agreement (Haacke) 11/01/2007 – 11/30/2009 0.24 calendar
National Football League $320,806
Neuro-imaging of NFL Retired Players
The major goals of this project are to process MR data from normal and TBI patients to visualize white matter damage and micro-hemorrhages.

MEDC 06-1-P1-0193 (Dong) 12/20/2006 – 12/31/2009 0.60 calendar
State of MI/MI Economic Development Corp. $617,157 (sub only)
HyperEye: Susceptibility Weighted Imaging-Bases Informatics Tool for Brain Tumor
The major goals of this project are to develop medical imaging systems with ready economical and technological applications, in which informatics tools use quantitative data extracted from medical images to help radiologist/physician make highly informed and accurate clinical decisions.

R01 AG011230-11 (Raz) 04/01/2005 – 03/31/2010 0.24 calendar
National Institutes of Health/NIA $18,085 (sub only)
Neural Correlates and Modifiers of Cognitive Aging
The major goals of this project are continuation and expansion of the research activities of the past 11 years to describe course of differential brain aging, mechanisms of differential brain shrinkage, age-related brain changes and approach to study of the biological and cognitive change.

H133G080064 (Hanks) 10/01/2008 – 09/30/2010 0.24 calendar
National Inst. on Disability and Rehabilitation Research $593, 022
Neuroanatomical Correlates of Positive Psychology Among People with Traumatic Brain Injury: A Biopsychosocial Model
The major goals of this project is to improve our ability to identify individual characteristics and resources that can be used to facilitate well-being and recovery of function after TBI.

NSF 06-597 (Dong) 06/01/2008 – 05/30/2011 0.60 calendar
National Science Foundation $276,618
CRI:IAD Acquisition of Research Infrastructure for Knowledge-enhanced, Large-scale Learning of Multimodality Visual Data
The major goals of this project are to purchase a major piece of equipment for data storage.

2R01HL062983-04A2 (Haacke) 07/01/2008 – 06/30/2012 2.40 calendar
National Institutes of Health $1,560,829
Susceptibility Weighted Imaging (SWI)
The major goals of this project are to continue the development of SWI to: a) make it more clinically viable by reducing phase processing artifacts; b) evaluate susceptibility itself by creating a susceptibility map of human tissue; c) study its role as a new MR angiographic method by simultaneously collecting MRA and SWI data; and d) speed up its acquisition time to less than 5 minutes for whole brain coverage, independent of any parallel imaging gain factor.

Master Research Agreement (Haacke) 07/01/2009 - 06/30/2012 0.60 calendar
Siemens Medical Solutions $300,000
The major goals of this project are to collect clinical data for SWI in the areas of trauma, stroke, and vascular disease.

K08 Mh079176A (Behen) 09/03/2007 – 07/31/2012 0.00 calendar
National Institutes of Health/NIMH $680,483
Structural and Functional Neural Correlates of Early Postnatal Deprivation
The major goals of this project are to evaluate the neuroanatomical correlates of early social deprivation (ESD) in human children using both state-of-the-art MRI and PET methods.

R01 NS041922 (Juhasz) 07/01/2008 – 04/30/2013 0.96 calendar
National Institutes of Health/NINDS $990,000
Longitudinal neuroimaging in Sturge-Weber syndrome"
The major goals of this project are to study the effects of Sturge-Weber syndrome on the brain over time.

Pending:

None.

Overlap:

No overlap for Dr. Haacke exists between the above grants and the current application.