White Paper on Brain Disorder Phenomenology Using Noninvasive Brain Analysis

Presented by

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I. Executive Summary

A. Proposed Work

We propose the formation of a scientific center of excellence for the purpose of developing and evaluating superconducting instrumentation and high fidelity computational electromagnetic brain models for the high resolution study of human brain activity. The proposed center will utilize the strengths and expertise of scientists in New Mexico, including physicists, engineers, and medical neuroscientists. Working together, this team will translate their knowledge in diverse areas such as superconductivity, cryogenics, electronics, image processing, computational electromagnetics, advanced signal analysis, and neuroscience to develop hardware, software, analyses, and medical applications for a new generation of brain imaging systems. Such imaging systems would consist of a 1000 sensor biomagnetometer, parallel supercomputer, and graphic workstation operating seamlessly to translate the brain's magnetic and electrical signals into a three-dimensional moving image showing it's instantaneous intensity and distribution. This instrument, coupled with advanced signal processing techniques and a computational electromagnetic brain model, will be used to study the brain in health and disease states. The knowledge gained in medical and basic science about the brain could be used to:

1. *Lower Health Care Costs:* Health care costs for neurological disorders can be reduced through the development and use of more specific and sensitive diagnostics.

2. *Minimize Surgical Risks:* The risk to critical areas of the brain may be reduced by identifying those areas noninvasively, and sparing them during neurosurgery.

3. *New and Improved Treatments:* We can improve the treatment of neurological diseases by using tomographic images of the brain's activity to provide immediate quantitative feedback of how the brain responds to that treatment.

4. *Psychiatric Disorders:* The proposed noninvasive brain imaging system and computational model will expand our understanding and treatment of mental illnesses.

5. *Basic Neuroscience:* The proposed center, instrumentation, and computational model will further our knowledge of the higher functions of the brain--the essence of what it is to be human.

The research instrumentation and computational electromagnetic brain model will be offered as a national resource center for the study of the brain. The technology developed for this biomagnetometer will be made available to U. S. industries, expanding our competitiveness in the international medical instrumentation marketplace.

B. Technical Benefits

In order to develop an advanced neuromagnetometer, we will need to develop technology in the following areas:

1. *Superconducting sensors:* Thin-film SQUID (Superconducting Quantum Interference Device) magnetic sensors will be designed to improve upon the sensitivity and dynamic range of existing designs. An all digital sensor design will reduce parts count that will improve manufacturability and enable us to expand the number of sensors without increasing complexity. SQUID sensor development has extended application in many areas of remote sensing, where the highest attainable sensitivity is of importance.

2. *Cryocoolers and Cryostats:* Cryocoolers and low loss cryostats will be developed so as to reduce the size and portability, while increasing the flexibility of existing dewars. Instead of relying on a large reservoir of liquid helium for cooling, we propose developing low temperature, high efficiency, long-life refrigeration systems, thus reducing the 1000 sensor array to a "hair dryer" enclosure. The cryocooler technology we will develop will also benefit other types of low-noise sensors and portable quantum standards.

3. *Image processing:* We will develop computer algorithms for three dimensional segmentation of medical images from CT or MRI scans. Specifically, processes will be developed and tested to automatically recognize the different tissue types in the brain--scalp, skull, dura, cortex, blood vessels, etc.--and create a model of each surface, layer by layer. This model will be used for electromagnetic calculations of the magnetic fields and electrical potentials resulting from brain activity. Automated image segmentation will also be valuable to radiologists, in that portions of the brain (as well as other organs) will be more readily visualized without the intervening tissue layers--i.e., as they might appear during surgery.

4. *Computational electromagnetics:* The segmented model of the various tissues in the head, known as a finite element model (FEM), will be used to provide a high accuracy prediction of the magnetic fields and electrical potentials resulting from the brain's electrical activity. This is called the forward solution. A highly accurate forward solution is necessary in order to compute a high resolution unambiguous estimate of the brain's activity. Because of the complexity of these calculations, software will be developed for high speed parallel computer systems.

5. *Signal processing:* What does one do with 1000 channels of brain signal information? The classical EEG notion of displaying each individual channel on a chart recorder is both impractical and wasteful of the rich information of such a large array. Instead, we propose deriving signal processing techniques from the array processing used in phased array radar. This would enable the array of 1000 sensors to be instantaneously "steered" to any part of the brain, receiving the brain's signals with much higher sensitivity and selectivity than any single sensor. The array could then be "scanned" through the three-dimensional volume of the brain, generating a tomographic picture of its activity. This type of signal

processing would also improve the array's rejection of magnetic disturbances, such that an expensive and bulky magnetically shielded room will no longer be required for neuromagnetic measurements.

C. Recommendations

The proposed project utilizes scientific and engineering expertise that is unique to New Mexico. Success in any single portion of this project can boost our technological competitiveness in the world marketplace. The 90's have been dubbed, "The Decade of the Brain." This work will advance a noninvasive technology from a laboratory curiosity to commercially viable instrumentation, lending that phrase new meaning. In three years, New Mexico will host an international meeting on biomagnetism. The proposed center will demonstrate our creativity and know-how to the world scientific community. This project has low risk and a large potential benefit to medicine and neuroscience. We therefore strongly recommend its approval.

D. Scientific and Engineering Research Partners

The scientific and engineering research partners for this effort consists of components from each of the following areas: Government, National Laboratories, Industry, and Academia.

Sandia National Laboratories brings experience in massively parallel supercomputer applications, cryogenic support systems, finite element modeling, and computational electromagnetics.

Veterans Administration/Center for Magnetoencephalagraphy brings experience in neurological phemeneurology, medical imaging, and has experimentation facilities.

The industrial partners would consist of IBM, TRW, and Conductus for SQUID design and fabrication alternatives.

The Academic partners consists of University of New Mexico, University of Houston, and the University of Arizona who collectively bring expertise in signal/image processing, finite element modeling for biological applications, radiological imaging, and neurology.

II. Introduction

In todays society brain disorders devastate the lives of 20% of the total population or approximately 50 million people. In monetary terms the per capita cost is $1690, which equates to approximately $400 billion per year or 7.3% of the Gross Domestic Product. This figure includes both direct costs such as medical treatement and services, and indirect costs such as lost wages and family caregiving expenses. In proportion the direct costs equal approximately one-fourth to one-half of the total ($104 billion in 1991) while the indirect costs make up the rest ($296 billion in 1991).

Brain disorders include well over 650 disorders that can be divided into three general categories. Psychiatric disease ranging from schizophrenia to cognitive impairment account for of $136 billion in costs. Neurologic disorders - dementia, mental retardation, multiple sclerosis, head and spinal cord injuries, stroke, cerebral palsy, and epilepsy - cost $103 billion. Disorders of addiction such as alcohol and drug abuse cost $161 billion. Some disorders such as multiple scleroses are killers and as a category, brain disorders are a leading cause of death in the United States today. They are the most common and severe cause of social, economic, and psychological disabilities in this country.

Empirical medicine has played a centrol role in understanding brain disorders. Much of the current medical knowledge relating to understanding brain function has relied heavily upon experiments conducted on surviving victims of unfortunate experiments of nature, such as stroke. In fact, most of what is currently known about the localization of normal language comes from the study of aphasia, a disorder of language that is found most often in patients who have suffered from a stroke or head trauma. Furthermore, almost everything we know about the anatomical organization of language and memory comes from clinical studies of patients with lesions of the brain. Today correlation of major mental illnesses to normal and abnormal brain activity is based primarily on postmortem studies, animal research, and the examination of peripheral metabolites in human beings. Ultimately one would like to somehow map the vast range of cognitive functions that become distorted or diminished, leading to brain disorders, by observing the structure and metabolic and neurochemical function of the brains of normal individuals.

Serious brain disorders including anatomical and functional disorders typically possess characteristically abnormal electrical signatures that can be directly determined or inferred through current measurement techniques. The current technology used in diagnosing such disorders are categorized below with relevant examples of each technology.

I. Active - Invasive: This category is characterized by requiring either direct access to the brain for stimulation or injection of radioactive sources that can be tracked by detectors.

Position - emission tomography (PET) is a nonsurgical technique that falls within this category. It provides images of brain function and has revolutionized the study of human cognitive processes and psychiatric and neurological disease. This emission tomography technique requires one to substitute position - emitting isotopes (half-lives ranging from several minutes to several hours) for constituents of biologically important compounds such as oxygen, carbon, nitrogen, and hydrogen. The specific isotope is then injected or inhaled by the patient and subsequently accumulates in specific regions of the brain according to metabolic activity. In the process of position emission the isotope produces two gamma rays that can be detected and used for imaging concentrations of the isotope within the brain. Thereby localizing brain metabolic activity that must have electrical counterparts. Because PET scanning relies on radiopharmaceuticals, it is unsuitable for routine testing or therapeutic monitoring.

II. Active - Noninvasive: This category is characterized by requiring either the use of energetic radiation or stimulated emission by constituent atomic nuclei.

X-ray computerized tomography (CT) allows one to explore the regional anatomy of the brain in normal subjects and in patients suffering from neurological disease. Developed in the early 1970's, CT is the oldest brain imaging technique. In contrast to conventional radiography, the CT scan distinguishes gray and white matter. It provides images of bone, brain tissue, and cerebrospinal fluid. Even structures within the brain can be distinguished. Because it reveals anatomical detail, computerized tomography has greatly expanded the clinician's capacity for diagnosis. Nevertheless, the views of the brain produced by CT are static, i.e., CT scans allow one to explore the structure but not the function of the brain. To produce images of the dynamics of the living brain, other techniques must be combined with CT.

Magnetic resonance imaging (MRI) is based on computerized tomography and has been used to explore brain function as well as structure. It is a powerful imaging technique that can distinguish different body tissues because of their individual chemical composition. MRI requires a subject to be exposed to a pulsed radio frequency signal superimposed on a strong magnetic field gradient. The pulsed field stimulates the atomic nuclei to emit radio waves at characteristic frequencies dependent on the nuclear species and magnetic field strength. The composite emission spectrum therefore contains spatial information. Reorienting the magnetic field gradient allows one to image concentrations of particular nuclear species.

III. Passive - Invasive: This category is characterized by requiring direct access to the brain in order to assess its activity.

Surgical procedures make up this category and very often generate useful data but involve substantial risk and expense to the patient.

IV. Passive - Noninvasive: This category is characterized by the sensing of source currents within the brain either through electric potentials on the scalp or extracranial magnetic field's. In terms of a patients perspective, this category represents the most desirable of all the options considered.

An electroencephalogram (EEG) is record of the electrical activity of large ensembles of neurons in the brain. It is obtained while a subject is sleeping, sitting quietly, or during specific sensory stimulation. The scheme is to place macroelectrodes over the top and sides of a subjects scalp and measure the electrical potential between active electrodes. The frequency content of the potentials recorded from the scalp of a normal human typically vary from 1-30 Hz and are not a result of action potentials but a result of extracellular current flow associated with summated synaptic potentials in the activated pyramidal cells. The problem with current noninvasive tests based on EEG measurements to assess electrical activity abnormalities appears to be with their inadequate spatial selectivity.

While EEG is the mainstay of passive - noninvasive recording of brain electrical activity, a relatively new passive-noninvasive technology is emerging for use in imaging the source currents of the brain. This technology is built around the magnetoencephalagram (MEG), i.e., a record of the extracranial magnetic field generated by the brain source currents and has many advantages over todays competing technologies. In this application, the instrument used to generate images of brain source currents is built from magnetometers based on superconducting quantum interference device (SQUID) technology.

SQUID based magnetometers are very low noise devices that can respond to millisecond scale activity and monitor magnetic fields one billion times weaker than the Earth's magnetic field. This level of sensitivity and resolution is required because the magnetic fields generated by brain source currents are typically 100 - 1000 fT in strength and extend from 0 - 1 kHz in frequency.

Clinical implementation of this technology would require a conformal array of SQUID sensors placed in close proximity to the patients head. The array would then register brain electrical activity during a monitoring session. By using beamforming and beamsteering techniques, familiar to phased array antenna technology, in conjunction with an accurate patient specific brain model one can image source current activity to within a few millimeters, depending on the size of the sensor array. Most imaging techniques currently being used are based on an idealized dipole source current model and a layered sphere model of the brain. In reality, however, brain source currents are distributed throughout regions of the brain. This beamforming and beamsteering technique is ideally suited to mapping distributed source currents.

Unlike the competing technologies discussed above, brain source current imaging MEG technology enables one to precisely associate brain function with underlying anatomic structure. By understanding normal neurological phenomenology it will be possible to quantify abnormal brain activity and the brain disorders that result. Consequently, this technology will directly impact the diagnosis of brain disorders such as stroke, epilepsy, Parkinson's disease, Alzheimer's disease, and head trauma. Furthermore, the ability to quantify abnormal brain activity directly impacts the development of new drug intervention strategies. Currently it is impossible to determine drug effectiveness noninvasively. Generally drug effectiveness is judged solely on the basis of behavioral changes which are notoriously unreliable and may take days or even months to develop. Moreover, measurements of drug concentrations in the blood stream frequently fail to indicate the drug concentrations at the brain cells where they are active. The best measurement is one that monitors the changes in brain activity directly, and preferably one that is passive-noninvasive. The ability to assess drug efficacy in a timely manner will significantly reduce the costs involved with bringing an experimental drug to market. Presently the average cost to achieve this is $231 million and 12 years.

One of the many promising clinical applications of the brain source current imaging technology is in the identification of the focal point of epilepsy in persons who are candidates for surgical removal of the epileptogenic region. Current diagnostic procedures, namely EEG, CT, MRI, and PET often yield inadequate information for accurately determining the location of the epileptogenic focus within the brain. So the competing technology to diagnostic biomagnetic imaging is an invasive diagnostic procedure involving surgical intervention using depth electrodes. These electrodes are inserted into the brain through holes in the patient's skull and the electrical signals are then monitored for long periods of time, 5-7 days. This procedure obviously comes at substantial risk and expense, $20,000-$60,000. Consequently, of the approximately 360,000 persons in the United States that are candidates for epilepsy surgery only a couple hundred a year are actually treated. If the epileptogenic region can be surgically removed, however, the patient may become completely free from seizures. Brain source current imaging MEG can decrease the need for surgical diagnostic procedures in patients with epilepsy by providing preoperative, noninvasive localization of the epileptogenic focus in three dimensions. It will also minimize the collateral damage associated with the surgical removal of the epileptogenic tissue. This would clearly reduce both the direct and indirect costs associated with epilepsy which next to stroke is the most common neurological disease: about 1% of the population suffers from epilepsy. There are approximately 55 epilepsy surgery centers throughout the United States and Western Europe that would directly benefit from this new biomagnetic imaging technology.

Although MEG machines on the market today are large and expensive, it is quite likely that future machines will be smaller, less expensive, and readily available in a much wider market. This will permit the dynamic biomagnetic activity of electrically excitable organs (most notably the heart and brain) to be routinely monitored quickly and noninvasively. The miniaturization of this technology will permit rapid mass-screening of numerous medical disorders. Many disorders, when detected in their very early stages, may be treated at a much lower cost and with much less patient suffering than when they become acute. In this manner, this technology may greatly reduce medical costs by providing very early detection of disorders long before they become clinical. Since no physical contact is required with the patient, these machines have the capability of screening patients rapidly for specific disorders once their capabilities are scaled-up from the present technological level. This proposed research will result in the machine improvements necessary to achieve this mass-screening capability. We anticipate that many private companies would then be interested in producing such machines commercially following a cooperative research and development activity with our laboratories.

The enormous commercial and research markets for this biomagnetic imaging technology has not gone unnoticed by foreign governments. In particular, Japan's Key Technology Center (JKTC) joined with ten domestic firms Hitachi Ltd., Sumitomo Electric Industrial Company Ltd., Takenaka Komuten Company Ltd., Shimazu Corp., Seiko, Inc., Daikin Industries Ltd., Yokogawa Electric Corp, Toshiba, Shimizu, and ULVAC Corp. to establish the "Superconducting Sensor Research Laboratory" a new laboratory that will develop SQUID technology for basic brain research. The specific objective is to develop a 200-channel SQUID based MEG instrument for noninvasive brain examination. The system will then be used in brain research including source current imaging and analysis of data. This laboratory was initially capitalized at 100 million yen, and then recapitalized at 6 billion yen over a six year period that began in March 1990. The laboratory is funded 70% of budget by JKTC (a satellite bureau of Japan's Ministry of International Trade and Industry, MITI) and the other 30% by the consortium of ten companies.

The future of cognitive neuroscience hinges on our ability to study the dynamics of the living human brain. MEG has become the "new" noninvasive imaging technique that can provide clinically applicable information on the health of the brain, heart, and neuromuscular system. It shows promise of being the most important source current imaging technique to impact medical imaging since the advent of MRI. It is clear that the United States must not lose the ongoing technological battle in this area for not only economic competitiveness reasons but also national security reasons.

III. Problem Statement

This section specifically defines many problems that can be directly addressed with the brain source current imaging MEG system described in the proposed effort.

A. Neurological problems

The improved ability to extract and pinpoint brain signals using advanced hardware and signal-processing techniques will have numerous commercial and military applications, only a few of which can be mentioned here. In the commercial sphere, the most significant anticipated applications are improved clinical diagnostic tests for functional brain disorders. According to the Health Care Financing Administration (HCFA), total annual healthcare related spending in the United States exceeds $400 billion. More than one-third of this total, or $150 billion, is spent on the diagnosis and care of 72 million Americans affected by neurological and mental health disorders. The majority of these disorders are functional in nature and are poorly understood. Despite immense expenditures, the diagnosis and care of those afflicted with these illnesses has been inadequate because in most cases no direct noninvasive and definitive test exists to effectively diagnose or monitor treatment. We believe MEG will provide the required test capability, provided techniques can be developed to readily measure spontaneous and stimulated brain electrical activity from specific places in the brain that are implicated in specific brain disorders. This is exactly the goal of our development of the instrumentation and signal processing techniques described in this proposal, and therefore this work has enormous commercial potential

To appreciate the range of commercial applications for an advanced neuromagnetometer, we have selected several significant examples:

1. Epilepsy

The first example is the surgical cure of epilepsy, which is a grossly underutilized therapy. This is mainly due to the high cost ($20,000 to upwards of $60,000 per patient) and invasive nature (electrodes are surgically implanted into the brain to record the location of abnormal electrical activity responsible for the seizures) of the presurgical evaluation. Conservative statistical projections indicate there are at least 360,000 patients in the United States meeting the criteria for epilepsy surgery: Their seizures cannot be controlled by drug therapy; they are severely incapacitated by the disorder, and the brain tissue responsible for their seizures is localized and could be removed without significant neurological or functional impairment. Yet, only a couple of hundred epilepsy surgeries are performed annually. MEG is currently being tested as a noninvasive alternative to the present direct cortical recording techniques, and it shows great promise. If we can accomplish the improvements in instrument design and signal-processing capability that we are expecting in Phase II, MEG should be able to routinely identify the source of single epileptic events in the brain. This will reduce the cost of presurgical evaluation by an order of magnitude and make surgical cure of epilepsy widely available throughout the developed countries of the world.

2. Stroke

Another important medical application is the possibility of assessing stroke damage during the acute phase when interventional therapy might be administered to prevent irreversible tissue damage. No noninvasive means exists today to evaluate the spatial extent of reversible brain damage, and therefore physicians are often reluctant to take risky therapeutic measures without reasonable assurance that they will benefit the patient. Again, a neuromagnetic brain imaging system offers the possibility to map out the three-dimensional regions of affected tissue by focusing on changes in spontaneous brain electrical activity that accompany an ischemic condition prior to tissue death.

3. Psychiatric Disorders

There is much interest now in the potential use of MEG to assess psychiatric disorders. Some of these disorders are known to be accompanied by abnormal spontaneous brain electrical activity, but the association is too tentative for useful diagnosis or therapeutic monitoring. Positron emission tomography has been shown to have diagnostic potential on the basis of abnormal patterns of metabolic activity that must have electrical counterparts. Because it relies on radiopharmaceuticals, PET scanning is an invasive procedure and is unsuitable for routine testing or therapeutic monitoring. The problem with current noninvasive tests based on EEG measurements to assess electrical activity abnormalities appears to be with their inadequate spatial selectivity. The 1000 channel neuromagnetometer should permit the spontaneous electrical activity of the brain structures known from PET and other means to be affected by the disorder to be measured directly, thus providing the necessary diagnostic specificity.

4. Head Trauma and Tumor

Head trauma and brain tumor may be associated with regional damage to the brain or to its blood supply. The proposed whole head functional brain activity imaging system should be able to detect many signs of brain injury that may not show up on anatomic (MRI or CT) scans of the head. For example, an injured region may be visualized as a "hole" in the brain activity image. Also, regions of pathological brain activity such as abnormally slow ("focal slowing") or abnormally rapid activity, such as may be seen on the boundary of a damaged or compromised brain tissue. A neuromagnetic image, taken very early after head injury and throughout the recovery period, may provide immediate feedback on the effectiveness of a particular treatment, and could lead to improved management of head injuries. The brain imaging system may also be able to detect signs that indicate tumor or other inflamation of the brain before they show up in MRI or CT scans. Early detection of brain tumors would have a big impact on reducing mortality, morbidity, and medical costs.

5. Learning Disorders

Learning disorders and dementias (Alzheimer's disease, and AIDs dementia, for example) have been studies primarily by behavioral (psychometric) testing and post mortem examination of the brain. More recently, tests have been developed to identify biochemical and genetic markers for some of these diseases. These categories are lumped together in this section for convenience and due to lack of quantitative evaluation of the roots of the observed behavioral symptoms. The proposed whole head brain imaging system can permit visualization of the actual brain activity of each individual while they perform cognitive or memory tasks. By studying and comparing the way the normal and the pathological brain operate, we may be able to improve pharmacological brain operate, we may be able to improve pharmacological treatment and rehabilitation programs.

6. Substance Abuse

Substance abuse represents a serious problem throughout the world. The advanced neuromagnetometer may be able to detect fundamental differences in brain activity between those who are prone to substance abuse and those who are not. In addition, it is likely that such a brain imaging system could be used to noninvasively identify individuals currently using alcohol or other drugs, without the need for blood or urine tests. Such testing could be of value for screening personnel involved in hazardous or high-security jobs for which impaired judgement may have dire consequences. Lastly, our ability to quantitate brain activity may lead to improved management and treatment of substance abusers.

7. Pre-Operative Evaluation

Functional localization of motor and sensory areas of the brain, including regions serving language can provide important information needed for planning neurosurgery. Pre-surgical knowledge of the physical/anatomical locations of brain functions will guide the neurosurgeon in the surgical approach so as to spare injury to critical regions.

8. Spinal Cord Injury

Spinal cord injuries are often accompanied by motor deficits (paralysis) and loss of sensation for regions of the body connected below the injured spinal segment. The state of the medical art being limited, a permanently injured spinal cord cannot yet be regenerated; the connections between the brain's motor cortex and the muscles are severed. Furthermore, the feedback to the brain for joint position and muscle tone may also be severed. The proposed neuromagnetic instrument will have the sensitivity and spatial selectivity to focus on, and extract in realtime, the signals from the motor cortex of the brain. It is therefore possible to use the brain activity corresponding to intentional movement to control a prosthetic device to effect that movement. Although development of a fully portable system is still only conceptual, the principles could be tested using the 1000 sensor MEG based system.

9. Drug Evaluation

A final medical example is drawn from psychopharmaceutical treatment and new drug evaluation. Since it is generally impossible to noninvasively determine the effect of drugs on specifically targeted regions of the brain, their effectiveness is often judged solely on the basis of behavioral changes which are notoriously unreliable and may take days or even months to develop. At best, they are only consequences of the direct action of the drug on the brain. Moreover, measurements of drug concentrations in the blood stream frequently fail to indicate the drug concentrations at the brain cells where they are active. The best measurement is one that monitors the changes in brain activity directly, and preferably one that is noninvasive. There is a clear and large unmet need that appears to be a promising commercial opportunity for advanced MEG technology.

B. Basic Neurological Science Problems

1. Cognitive Neuroscience

Cognitive neuroscience has, in the past, relied heavily on localizing brain activity selected at a specific time latency relative to a signal averaged response. Signal averaging is, of course, useful for enhancing signal-to-noise ratio, but masks the trial to trial variations in the brain's response. In addition, as we select longer latencies from the synchronizing stimulus, the brain's response may have much weaker time-lock (vary in time delay), rendering signal averaging useless. The more important brain processes that distinguish humans from lower animals — language, imagination, and problem solving — are not readily locked to any external stimulus and will require more advanced types of signal processing to extract the desired signals from the background brain activity.

2. Lie Detection

Present lie detectors are notoriously unreliable because they are unable to test the origin of the autonomic response resulting in measurable physiological phenomena. The location-specific recording of spontantaneous brain activity offered by the advance instrument should more clearly reveal the brain's uncontrollable basic response to interrogation.

3. Man-Machine Interface

Among the potential commercial military applications of an advance MEG system is the assessment of human mental performance under conditions of high work load. These measurements may lead to improved design of the man-machine interface by more effectively conveying essential information to the brain such that the mental work is reduced. A more speculative but somewhat related application is the possibility that an MEG array focused by advanced signal processing (adaptive beamforming) to a specific brain site could be used to control a machine by directed mental activity alone. This could lead to an entirely new interface between man and machine. Another commercial military application could be screening personnel for exceptionally demanding jobs. Some individuals are clearly better suited for some mentally stressful tasks, such as piloting a fighter aircraft in combat conditions, than others. A reliable early test could save significant money spent on candidates who are unable to complete the final stages of their training due to latent inability to meet the demands of the job. Screening personnel for high security positions could also be an application of military importance.

IV. System Requirements and Design Goals

A. Sensor System Requirements

The sensor array must have full head coverage. The sensors must be spaced closely to one another (approximately 10 mm center-to-center) so as to maximize spatial accuracy. The sensors, operating at 4 K should be spaced as close as possible to the head. Present commercial systems have a 15 to 20 mm spacing. Reducing this to 5 mm through good cryogenic design will improve signal-to-noise ratio by almost 20 dB. The SQUID sensors must have high linearity, wide dynamic range, and low noise. All these factors are key to reconstructing images of the brain's electrical currents. The sensor array must also be able to discriminate against background ambient magnetic noise, and operate within a hospital environment.

B. Computational Electromagnetics Model Requirements

Imaging the continuous electrical currents of the brain requires high accuracy in computing the forward solution for magnetic fields and electrical potentials for any distribution of current in the head. This can be accomplished by creating a finite element model (FEM) from an anatomical scan (MRI or CT) of the head of each patient. The system must be capable of segmenting the anatomic image into regions of each tissue type (e.g., scalp, skull, dura, cortex, white matter, cerebrospinal fluid, etc.). By assigning a conductivity value to each of these regions, an accurate forward solution may be obtained. The image segmentation should be "turnkey" — that is, performed with little or no human intervention. The segmentation of an MRI or CT scan into a three-dimensional model, alone, would have significant medical value in the visualization of anatomic features.

Segmentation of the brain's cortical surface will further improve the computation of an image of the brain's electrical activity. First, the cortical layer is the source of the dominant primary currents and activity (it is the layer of the brain containing the neurons and their dendritic input connection). No significant sources should lie outside this cortical layer. Next, the electrical current vector is known to flow at right angles to the cortical surface. By knowing the local normal vector to any part of the cortical surface, we can reduce the number of unknowns in the image to just one — the current amplitude. Without this normal vector, there are three unknowns for the X, Y, and Z current amplitudes.

C. Supercomputer Requirements

The typical volumetric MRI scan is composed of an array of 256 by 256 by 128 voxels (volume picture elements), each with a dimension of 1 by 1 by 1.5 mm. Segmenting these 8.4 million picture elements requires a computer with a large memory capacity and high speed. Once the image is segmented, a finite element model can be constructed. Assuming a model volume of about 3000 cm^3, and a required localization accuracy of less than 0.5 cm, it is obvious that the FEM must contain at least 24,000 elements. Computation of the forward solution from this FEM will require large memory capacity and high speed. In a clinical setting, it is desirable to be able to compute complete images in under 5 minutes. This "benchmark" is roughly the time it takes to process an X-ray film. Computation of spontaneous brain activity at a specified location (simulating an invasive depth electrode) must be computed in realtime.

D. 4th Generation Brain Activity Imaging System Design Goals

The overall goal of this aspect of the project is to develop an instrument capable of generating a moment-to-moment image of the brain's electrical activity. To accomplish this, the instrument must measure the magnetic fields generated by the brain over the entire head with high spatial resolution. Based upon a sensor spacing of approximately 1 cm, this will require on the order of 1000 independent SQUID sensors.

Using present manufacturing practices, it is impractical to scale the current MEG system designs to 1000 channels. Analog dc SQUID sensors require a minimum of four wires (excluding the superconducting connections to the sensing coils) — two for bias and two for modulation and feedback — to connect with their room temperature flux-locked loop (FLL) electronics. These connections, which go from 4.2 K to 300 K represent a significant thermal load to the SQUID dewar/refrigeration scheme. Furthermore, it will be necessary to address the cross-talk between channels arising from the close proximity of these leads to one another. Even if we were to presume that such a system could be built using current techniques, the cost — on the order of $50,000 per channel — would make a 1000 channel system unmarketable. Clearly, in order to engineer the next-generation MEG system, we must address questions of cost and manufacturability.

Experimental all-digital thin film dc SQUID magnetometers have been demonstrated by several laboratories. The most noteworthy example was developed by Fujitsu, implementing the entire flux-locked loop on a single superconducting integrated circuit chip. This digital SQUID requires only three wires — bias, pulse output, and common. Since the bias and pulse output lines may be digitally multiplexed, a practical all-digital SQUID can significantly improve the thermal design by reducing the number of wires per channel going from 4.2 to 300 degrees K, and reduce crosstalk by virtue of a digital rather than analog output. The all-digital design also eliminates much of the room-temperature electronics, including the data acquisition subsystem. Furthermore, the input (sensing) coils would be integrated "on-chip," eliminating the need for superconducting interconnects, thus increasing reliablility. Development of a single chip digital SQUID magnetometer could be the key to making large array MEG systems commercially practical.

The cryogenic support of the current generation of commercial MEG systems consists of a dewar in which the dc SQUIDs and sense coils are immersed in a bath of liquid helium. The evaporation of liquid helium provides the refrigeration for the SQUIDs, which must be maintained below 10 K to be superconducting. A helium dewar system requires periodic replenishment of the liquid cryogen, and also poses limits to the degree to which the dewar and SQUIDs may be tipped in order to position the system around the head. Closed-cycle refrigeration of a dc SQUID magnetometer, using a Joule/Thompson heat exchanger has been successfully demonstrated using commercially available refrigeration components. In order to keep the proposed 1000 channel neuromagnetometer as small as possible, it will be necessary to develop a low-noise closed-cycle refrigeration scheme — a cryocooler — eliminating the need for a liquid helium reservoir large enough to immerse all sensors.

The Earth's magnetic field is approximately 1 billion times larger than the brain's magnetic signals, which are about 5×10^{-13} T peak-to-peak. In a typical city hospital, electrical machinary and ferrous objects moving in the Earth's magnetic field result in magnetic noise on the order of 10^{-7} T peak-to-peak. Many commercial neuromagnetometer designs include a magnetically shielded room as part of their system. This shielding attenuates the magnetic noise to levels low enough for the brain's MEG signals to be seen. However, a magnetically shielded room adds about $500,000 to the cost of an MEG system. Canadian Thin Films (CTF) has demonstrated a SQUID neuromagnetometer that does not require a shielded room. Using wide dynamic range digital SQUID electronics, they use noise reference channels to sample and subtract the ambient magnetic noise. A wide dynamic range design and adaptive noise reduction must be explored in the 4th generation MEG system design.

What does one do with 1000 channels of information? The traditional approach borrowed from EEG — displaying individual channel time series on a strip-chart recorder — is impractical. Furthermore, conversion of the MEG data into single and multiple equivalent current dipoles (misleadingly referred to as "magnetic source imaging" by some companies) discards most of the information obtainable from a large array MEG system. To address this, we propose using beamforming and beamsteering methods, a procedure borrowed from the processing used for large phased array antennas in radar and radio. This technique will permit us to estimate a three dimensional image of the instantaneous electrical currents throughout the brain. In addition, the electrical activity in any location within the brain could be examined *as if an invasive depth electrode had been implanted there.*

In order to compute accurate high-resolution tomographic images of brain activity, the precise shape of the head, together with that of each tissue layer (scalp, skull, dura, cerebral cortex, etc.) must be known. Thus "turnkey" software must be developed for automatically segmenting MRI or CT images of the head into a finite element computer representation of each different tissue layer. It is this finite element model that enables us to compute the magnetic fields and electrical potentials due to the electrical activity generated by the brain. It is expected that a low-end parallel supercomputer will be required in order for image segmentation and FEM compution time to take less than 5 minutes.

Computation of an image of the source current distribution using the measured magnetic fields and will also be programmed on a supercomputer. A time-moving image of brain activity will be computed frame by frame. The source current images will be "fused" with the anatomic image of the brain, thus enabling the viewer to see the relationship of the brain activity with its corresponding anatomic structures. A graphics workstation will be used to permit flexible display of the fused images. Selection of an anatomic coordinate from the brain image will allow selective display of the time-changing brain activity waveform that was estimated for that location.

Clearly, the development of such an advanced neuromagnetometer will require a systems engineering approach. Developing processes for improved sensors and cryogenic support are important, but don't constitute a whole system, whose design will guide potential manufacturers in production techniques needed for the next-generation neuromagnetometer.

V. Proposed Effort

The proposed effort consists of two phases. In the first phase we will undertake risk reduction experiments that will lead to the development of a small-scale near realtime MEG based imaging system. While this instrument will not give simultaneous full-head coverage, it will constitute a proof-of-principle instrument and will enable the second phase of the proposed effort. In the second phase we will implement the full-scale instrument design that minimizes the associated risks as identified in Phase I. The second phase will end with a full-scale demonstation of a near realtime MEG based imaging system.

The configuration of the full-scale MEG imaging system is shown in Figure 1. The cryogenic assembly is positioned over the patient's head. It contains the array of SQUID magnetic-field sensors, which spans the entire scalp and must be closely aligned with it, along with the cryogenic pickup electronics. An alignment subsystem monitors and adjust the position of the assembly relative to the head. The low-level signals from the pickup coils are brought out to a bank of room temperature amplifiers, then sampled and digitized by the acquisition subsystem to create digital data files which are stored on a host computer. The host provides a user interface for control of system parameters such as amplifier gain and sampling rate. It also serves as a front end to a parallel supercomputer which calculates the extracranial magnetic fields due to a point source using the electromagnetic brain model (constructed from auxiliary data such as MRI scans) and uses these results, along with the SQUID data, to compute maps of brain activity in space and time. The host, under user control, post processes the maps and feeds them to a display subsystem. The system software also provides for system calibration using test inputs developed from SQUID measurements of simulated brain-like signal sources, i.e., phantom measurements.

Figure 1. System configuration

Phase I of this project will include a detailed, end-to-end proof of principle. We will develop prototype computer codes for electromagnetic brain modeling and activity mapping, and we will acquire the supercomputing resources needed to run these codes rapidly. The algorithms will be based on realistic models of brain signals derived from patient specific brain data. Analyses and simulations will establish the capabilities, such as number of channels, sensor spacing and noise floor, that the full-scale MEG system will need to make useful whole-brain maps of the phenomena of interest.

To facilitate brain data collection necessary for Phase I proof-of-principle experiments, a state-of-the-art MEG system (37 channels or more) will be procured and installed at the VA Medical Center in Albuquerque. Although such a system does not provide simultaneous whole-head coverage, nor adequate sample density to measure all types of brain activity in a clinical setting, it is valuable as a source of research data from which space-time profiles of important brain events can be generated. Today's state-of-the-art models of brain activity are much too crude to yield predictions at this level of detail, and so cannot serve as a guide to MEG system design. Once the empirical profiles are found, they will be expressed as computational models suitable for analysis and simulation.

A computational electromagnetic model of the brain is needed to predict what data a signal of known profile will produce in a MEG sensor array of known configuration. This is referred to as a "forward" model, and is a necessary part of the "inverse" model which reconstructs the brain activity from a given set of sensor data. The brain signals can be thought of as current sources ("primary currents") which induce "secondary" return currents that obey Ohm's law. These currents produce magnetic fields as described by the Biot-Savart law; each SQUID sensor measures a component of the total field at a point in space. The task of the forward model is to compute the magnetic fields, given the primary currents. In most models, the head is treated as a set of concentric spheres, for which the field can be expressed by an analytic formula. The errors in such a model are unacceptable in a system that is to localize the measure the primary sources with high accuracy, because they cause high-performance inversion algorithms to fail. With a realistic electrical model of the head, no analytic solution is available; the field must be computed numerically. As part of the proof of principle, we will develop codes to compute a 3-D finite-element model tailored to the shape of each patient's head, as derived a priori from auxiliary data such as an MRI scan. The code will be validated, first through tests on standard shapes with known analytic models, and later through comparison to data collected on phantoms. An existing parallel supercomputer, belonging to Dept. 9735 at Sandia, will be upgraded as necessary to run the codes at a speed sufficient for large-scale simulation and testing.

To provide clinically relevant data requires both timely and accurate patient specific brain information. The ability to accurately image brain source currents is dependent on having an accurate forward solution. The forward solution consists of solving for the extracranial magnetic field generated by a localized source current within a brain model. In order to generate an accurate forward solution the brain model will be generated directly from patient specific anatomical data gathered through a standard MRI session. During Phase I and using the MRI data we will demonstrate that (1) a detailed finite element mesh of the brain can be constructed and (2) the appropriate electrical characteristics of the brain media can be estimated. To accomplish this in a timely manner will require an automated data segmentation procedure that can accurately extract boundaries of the five different media which comprises the brain. The multiple MRI data segmentation tasks will be accomplished through a static decomposition on a parallel supercomputer for high parallel efficiency. Necessary electrical properties of the various brain media will be extracted directly from the MRI data. Once the boundaries and electrical characteristics have been determined a 3-D finite element mesh, the brain model, will be generated. Within the brain model one can now place a localized current source. The extracranial magnetic fields generated by this current are then computed using the parallel supercomputer and used to guide the beamsteering algorithm to a specific site within the actual brain (MEG) data space. By moving the current source around in the brain model one can localize, i.e., map the actual brain source currents contained within the MEG data.

We will undertake analysis and computer simulations to assess the usefulness of an MEG sensor array as a noninvasive probe of brain activity. Such a probe must take accurate measurements over time of currents within a small, localized portion of the brain. Interfering signals from other parts of the brain must be suppressed, along with signals from sources outside the head such as RF interference from electronic equipment. The effect of random noise within the MEG sensors must also be kept low.

Given a MEG based imaging system, the key to accurate localization of brain activity then depends upon the signal processing techniques implemented. The signal from the desired region appears at each of the MEG sensors with a strength that depends on its location within the brain. The signal processing algorithm must combine the sensor outputs in such a way as to reproduce the desired signal while suppressing noise and interference. It relies on the forward model of sensor gain vs. location in making the combination. The model is adjusted to an individual patient using the same auxiliary data used in finding the head shape, to create a "brain atlas" showing the region of possible signal sources. To avoid the high cost of human interpretation, the atlas must be created by an automatic process involving segmentation of the auxiliary images to identify regions composed of tissues of different types. This is a classic computing problem for which a variety of promising approaches exists. Guild members from the University of New Mexico will develop image segmentation methods specific to the MEG problem. These will be combined with the computational electromagnetics codes to create a system capable of solving the forward modeling problem rapidly.

Given a forward model, the "inverse" problem of reconstructing the brain activity from the MEG sensor outputs is solved by computing an ensemble of weighted linear combinations of the sensor outputs. Each combination is an estimate of the activity vs. time in a small region of the brain, and its weights are chosen to select activity in that region while suppressing activity elsewhere in the brain and interference from outside the head. The problem of choosing the weights is analogous to the problem of beamsteering in array antennas. Its solution is aided by the fact that over short periods of time, only a small fraction of the region of signal sources is active. This makes possible the use of concepts from the theory of adaptive arrays, in which the location of interfering sources is estimated from the data and the array weights chosen to direct antenna pattern nulls at the interfering sources. Techniques of this kind have been used successfully to enhance data from existing MEG systems. Guild members from Sandia, the Veteran's Administration, and other laboratories will develop algorithms for the inverse problem on large arrays, using brain data to refine the reconstruction model. These codes, combined with the forward solution codes, will make up the prototype of an end-to-end capability to compute maps of brain activity vs. space and time from MEG and auxiliary input data.

As the algorithms are developed, they will be incorporated into analyses of the performance of candidate MEG sensor configurations. Simplified models will be used to identify the most promising candidates, then detailed simulations will be used to choose the configuration preferred for full-scale development.

A. Hardware System Development

The proposed design approach will work from the bottom up and from the top down simultaneously. Clinical information obtained from the Phase I study using existing 37 channel MEG machines and improved source reconstruction algorithms will be used to predict the minimum sensor density necessary to detect various brain functions and to diagnose various disorders. While this is underway, a second study will determine the maximum number of brain sensors which may be supported by a fixed level of supercomputing support. Although the optimal number of brain sensor channels will be determined from these studies during the first phase, we anticipate the optimum number will be about one thousand. These studies will consider two different operating scenarios; one which provides near realtime information with no more than a 5 minute delay, and the other which accumulates data on the evoked cortical response due to repeated stimulation. The first mode of operation, which will be genuinely new for MEG, should prove useful in rapid mass-screening for particular disorders. It should also prove useful during useful during certain surgical techniques. The second scenario will expand the capabilities of previous MEG machines, providing greater utility to drug action studies and to the brain's functional mapping. Although these initial designs are optimized for brain research, the design will remain flexible so that it may be re-deployed for other research, such as heart and fetal studies.

B. Machine Design Issues

Today, commercially available MEG machines are limited to a maximum of 37 channels. Canadian Thin Films, Inc. plan to introduce a 90 channel system soon, and Neuro Mag, Ltd. of Helsinki, Finland have recently reported their successful testing of a 122 channel system. Japan's MITI are attempting to develop a similar machine with at least one hundred channels designed for full-cortex coverage. Considering the current state-of-the-art it is apparent that this proposed 1,000 channel MEG system will represent a dramatic increase in the overall system complexity. As discussed below, this increase in system complexity will mandate a genuinely new system architecture which permits a much more dense packing of sensor channels, and which utilizes novel new cryogenic support designs which will permit low-noise operation in any orientation of the MEG sensor array. As such, we propose a number of risk reduction experiments during the first phase designed to define the optimal approach for increasing the density of sensor channels in the proposed super-MEG machine. Two different technical approaches will be pursued to optimize the SQUID and sensor configuration initially. The first, lower-risk approach will determine the optimal method of close-packing conventional thin-film analog SQUID amplifiers and their associated micro-lithographic sensor coils at the density required in this super-MEG machine. The second approach, entailing higher risk and a much higher potential benefit, will pursue technical improvement of a new class of digitally biased SQUIDs which have only recently been developed, primarily by Fujitsu in Japan. We anticipate that this second approach will rapidly close our existing technical deficit, relative to Japan, in this emerging new SQUID technology, which should prove useful in many civilian and military applications, as well as in the proposed MEG work. After 15 months, the optimal SQUID and sensor technology will be selected and integrated into the overall super-MEG system design. These risk reduction experiments, together with others related to the system's cryogenic and thermomechanical design, are described below.

C. SQUID Risk Reduction Studies

As more sensors and SQUID amplifiers are packed into a limited surface coverage about the human cortex, problems associated with channel cross-talk and bias/feedback sub-system interference become a major limitation to continued system expansion. Recently Fujitsu has begun an extensive program, coordinated through MITI, focused on the development of digitally-biased SQUIDs in which all feedback and readout functions are facilitated on the same integrated circuit as the SQUID and sensor coil. Although this technology could solve many of the high-density packing problems mentioned above, overall noise level and other system integration issues greatly limit its utility at this time. Improvement of this technology for incorporation into the super-MEG system is considered high-risk, however, the remaining technical developments necessary to make this technology viable seem readily achievable. A series of risk reduction experiments designed to utilize these new SQUID devices will be pursued, together with less risky experiments which use conventional analog SQUIDs with room temperature biasing and feedback electronics. At the end of these experiments, and at the culmination of the first phase of this proposed research, we anticipate that the final super-MEG system design will utilize an optimized hybrid of these two SQUID design concepts.

Numerous domestic manufacturers of thin-film SQUIDs are capable of producing the channels which utilize conventional, analog SQUID technology. Firms such as IBM, Quantum Design, Conductus, BTi, Hypres, and possibly others would be potential contractors for this aspect of the work. In order to minimize the SQUID cross-talk at our required high density of sensor packing, we will issue a contract to at least one of these firms (during the first phase) to produce a miniature fifty-SQUID sensor array at this packing density. This will permit the materials and micro-lithographic designs to be optimized to minimize cross-talk and feedback channel interference to the incoherent noise level. These small contracts executed during the first phase will greatly reduce the technical and business risks associated with the super-MEG machine development during the second phase.

The higher-risk digital SQUID technology will also be pursued aggressively during the first phase. TRW owns the basic digitally-biased SQUID patents within the United States, and as such we will attempt to team with them in all such efforts. Fujitsu, with extensive funds from Japan's MITI, have taken the world lead in digital SQUID technology. Fortunately, Fujitsu has been very open with this technology through numerous publications. Fujitsu's scientists seem willing to collaborate with their USA colleagues, so we propose to place a physicist at Fujitsu's development laboratories to work with their lead physicist, Dr. H. Fujimoto, during the first phase of this development. We know of two physicists, both fluent in Japanese and USA citizens, who may be interested in this position at Fujitsu through a contract with their current employers. This physicist may act as a technical liaison, conveying technical information from the MITI laboratories in Japan to firms in the USA such as Sandia and TRW. Once the basic self-contained digital SQUID sensor has been developed, we will study the way in which they may be close-packed, in a manner similar to the study with analog SQUIDs described above.

D. System Integration Developments

The first two sets of risk reduction studies outlined above involve the optimization of the basic SQUID and sensor design. In essence, this aspect of the system development centers on optimizing the basic "building block". System integration and cryogenic support studies will also be conducted during the first phase in order to determine the optimal method of thermo-mechanical support of the very large array of sensors in the super-MEG machine.

Recent advances in closed-cycle cryogenic refrigeration technology have resulted in dramatically longer intervals of highly reliable continuous operation (typically 20,000 hours), and in astounding cost reductions, both in purchase price and operating costs. New cryogenic designs which integrate the SQUID and sensor array into a plenum structure which serves as the closed-cycle refrigerator's lowest temperature heat exchanger will permit operation of the super-MEG machine in any orientation. This will greatly increase the clinical utility of these machines.

Present day MEG machines locate the fifty liters of liquid helium, which maintain the SQUIDs and sensors in their superconductive state, directly over the patient's head. This primitive cryogenic design, which Newsweek referred to as the "Hair dryer from Hell" in their April 20, 1992 issue, uses gravity to stabilize the liquid helium under its vapor throughout the clinical measurements. Any repositioning of the apparatus above the patient's head requires a cumbersome relocation of this large apparatus on a hefty overhead supporting transit system. Such motion inevitably creates a sudden increase in the liquid helium boil-off rate, resulting in a loud hissing sound as the cold helium vapor escapes from the system's check valves. This process is disruptive even to healthy humans, and it is often absolutely terrifying to patients afflicted with major psychiatric disorders such as paranoid schizophrenia. The new cryogenic support systems to be incorporated into the super-MEG machine will operate silently in any orientation. The space saved by removing the liquid helium storage volume should permit the thousand-channel super-MEG system to occupy less overhead volume than existing 37-channel systems.

E. Thermo-Mechanical Risk Reduction Experiments

The development of this integrated cryogenic support architecture will involve the construction of micro-lithographic arrays of SQUIDs and superconducting sensor coils which are supported by thousands of thermally-conducting electrical feed-throughs protruding from the refrigeration plenum. These feed-throughs will provide the electrical contracts to the SQUID and sensor arrays, together with the cooling necessary to maintain these arrays in their superconductive state. A fifty-channel prototype of this design at a packing level equal to the super-MEG design, shall be developed during the first phase of this effort to reduce the technical and business risks during the full-scale, second phase construction. We anticipate that these risk reduction experiments, together with the overall integrated design development, will be performed within Sandia.

The closed-cycle refrigerator which will maintain the integrated plenum and SQUID/sensor arrays at or below 5 Kelvins will be located away from the immediate clinical environment. The refrigeration cold head will be located about four meters from the super-MEG array, possibly in the pipe chase adjacent to the MEG room. An evacuated and super-insulated flexible hose shall connect the refrigeration cold head to the clinical MEG assembly. The refrigeration cold head will have a total mass of about 15 kg. It shall be supported by a 100 kg helium compressor which may be located an arbitrary distance from the cold head, say in a utility shed. Concepts similar to this design have been successfully proven in other superconductive device applications within Sandia, and as such no first phase risk reduction studied need be undertaken.

The optimal design for the refrigeration cold head is evolving rapidly at this time. For this reason we shall evaluate numerous competitive designs during the first phase to optimize the final cryogenic system's reliability and efficiency. Manufacturers of these new and vastly improved closed-cycle 5K refrigerators within the USA include Boreas, RMC, Tristan, CryoMech, and possibly others. Since the superconductive electronics dissipate little to no heat while they operate, this super-MEG design requires only a modest amount of cooling power to maintain a temperature below 5K. Hence the closed-cycle refrigeration development aspects involve only a reliability study and little to no additional engineering development.

Figure 2. Proposed Project Organization

In Phase II, we will design and fabricate a full-scale MEG array system, capable of localizing and measuring electrical signals over the whole brain with the maximum precision allowed by the laws of physics. It will contain on the order of 1000 SQUID sensors, in an array spanning the entire scalp. The computational models, understanding of brain activity, and sensor technology developed in Phase I will serve as the basis for the design. Once completed, the system will be installed at the VA Medical Center in Albuquerque to serve as a national resource for research into brain function and brain disorders.

The fifty-channel prototype sensor built under Phase I will be installed at the VA at the start of Phase II. Collection of brain data will continue throughout this phase. The fine spatial resolution in this system will make it possible to extract more detailed and accurate signal profiles than those found in Phase I. A library of profiles will be incorporated into the computational model as part of the initial operational capability for the full-scale system.

The computational model and mapping algorithms will be revised based on the experience of Phase I. We will acquire a parallel supercomputer, of the highest performance commercially available, to run the codes. The software configuration will make use of the parallel computer's ability to allocate processing power dynamically as the task load changes. The forward model will be made more detailed (size increased from 24,000 elements to approximately 1 million) to achieve the necessary model quality at high spatial resolution. The inverse model will be revised and recorded as necessary to accommodate the large number of sensor channels. All the codes will be integrated to create a system capable of computing MEG scan results in a timely manner (one hour from start of auxiliary scan to finished output).

The hardware design of the full-scale sensor will be finalized early in Phase II, with the rest of the time devoted to fabrication, assembly and integration. Fabrication of microelectronic components will be done at Sandia's Microelectronics Development Facility, at contractors facilities, or some combination. The cryogenic subsystem will be built at Sandia, and assembly and integration will be done there.

VI. Proposed Costs and Schedule

This section gives the proposed costs and schedules. The effort would be managed by Sandia National Laboratories with the Veteran Administration MEG Laboratory being a core laboratory along with Sandia. Sandia will develop contracts with the University of New Mexico to work in image analysis and to advise on some aspects of neurological sciences, Los Alamos National Laboratory for basic sensor research, the University of Houston for computational electromagnetics, the University of Arizona to consider machine interfaces for surgical procedures, and other industrial entities for both sensor and computational electromagnetics research.

The proposed funding profile is as follows:

A. Phase I
  1. Core Laboratories
    a. Sandia National Laboratories

1) Supercomputer Upgrade	2M
2) Inital EM Brain Model Developement	3M
3) Initial Sensor Array	4.5M
	9.5M

    b. Veterans Administration

1) MEG Acquistion and Installation	3M
2) Research	0.7M
3) MRI Time	0.1M
	3.8M

  2. Universities

a. UNM (EECE Dept.)	300K
b. University of Arizona (Neurology Dept.)	500K
c. University of Houston (EECE Dept.)	100K
	900K

  3. Others

a. Ochsner's Clinic	200K
b. Los Alamos National Laboratory (Device Research)	500K
c. McDonnell-Douglas (CEM Consultant)	400K
d. IBM (SQUID Research)	500K
e. TRW (SQUID Research)	500K
f. Other consultants	300K
	2.4M

Total Phase I - 16.6M

B. Phase II
  1. Core Laboratories
    a. Sandia National Laboratories

1) Supercomputer and Workstation Acq.	8M
2) Final EM Brain Model Development	6M
3) Final Sensor Array	14M (includes subcontracts)
	28M

b. Veterans Administration (Research)	2M

  2. Universities

a. UNM (EECE Dept.)	600K

b. University of Arizona (Neurology Dept.)	1.5M
c. University of Houston (EECE Dept.)	200K
	2.3M
3. Others	
a. Ochsner's Clinic	400K
b. Los Alamos National Laboratory (Device Research)	1M
c. McDonnell-Douglas (CEM Consultant)	600K
d. Other consultants	1.1M
	3.1M

Total Phase II - 35.4M

Total 3 year program cost $52M

Appendix: Domestic and Foreign Capabilities

A. Existing U. S. Capability--Manufacturers

BTi, San Diego, CA

Founded in 1970 as S.H.E. Corporation, BTi introduced the first commercial SQUID sensor and electronics. In 1980 they introduced the first commercial dc SQUID system, BTi is considered the world leader in commercial SQUID systems, supplying SQUID sensors, electronics and dewars for laboratory use along with geophysical magnetometers and biomedical gradiometers. BTi's most complex SQUID system is a 37-channel gradiometer array for biomagnetism that includes 8 additional SQUID channels for electronic noise cancellation ($2,200,000) with a system noise 10 fT/. BTi has also delivered single channel dc SQUID biomagnetometers operated by a closed cycle refrigeration system (hybrid Gifford-McMahon/Joule-Thompson) with a system noise 20 fT/. Although BTi has a DARPA/ONR contract to do research on and fabricate high T_c SQUIDs, BTi's current thrust is purely biomedical. In July 1989, BTi went public, with a market valuation of ~ $50,000,000. In January 1990 Sumitomo Metal Industries, Ltd. of Tokyo became BTi's Asian distributor. As part of that arrangement Sumitomo purchased 12.9% of BTi, along with two 37-channel biomagnetometers to be placed at development sites in Japan. BTi currently employs 135 people of which half are involved in the development of SQUID devices. BTi operates a subsidiary in Aachen, W. Germany (S.H.E. GmbH) to handle European sales and service. Sales for 1989 were $8,100,000, with a projected growth of 30% annually.

Quantum Design, San Diego, CA

Privately held, QD was founded in 1982 by four former S.H.E. employees supplying SQUID electronics and systems. Their major product is a SQUID susceptometer, accounting for more than 80% of their sales. QD has developed 200 MHz rf SQUID electronics that achieve 35 mF_0/ (using BTi rf SQUID sensors). They also manufacture BTi style 20 MHz electronics with a noise level of 100 mF_0/. A subsidiary, Quantum Magnetics, is the R&D arm of QD being primarily concerned with new product development and custom systems. QD currently buys rf SQUID sensors from BTi, but now has capability to produce dc (and rf) SQUIDs of their own design. One interesting feature of their design is the ability to desensitize the SQUID sensor by factors of 100 or more (e.g., to 10^{-26} Joules/Hz). Custom systems supplied by QD include a SQUID magnetometer with 3 m spatial resolution, systems for detection of corrosion currents and a 6-element airborne gradiometer system. QD is the subcontractor to IBM on NCSC, Panama City 8-element array refurbishment. As part of this project, they have developed compact dc SQUID electronics that operate at the 5 mF_0/ level (using BTi dc SQUID sensors). Current research activity (SBIR funded, pointing towards commercial exploitation) include development of magnetometers for corrosion measurements (NDE) and SQUID NMR for explosives/drug detection. Estimated revenues for 1989 were $10,000,000. These revenues are not expected to increase because of market saturation of their principle product, the model MPMS SQUID susceptometer. QD currently employs 80 people. European sales are handled through S.H.E. GmbH.

2-G Enterprises, Palo Alto, CA

Basically a garage shop outfit, they have two decades experience in constructing SQUID systems. Their principle product is a rock magnetometer. They are also a manufacturer of SQUID systems to various government agencies. Normally, they supply their own rf SQUID sensors and electronics, but have supplied systems with BTi SQUIDs. Estimated revenues for 1989 were on the order of $ 1,000,000.
Systems Integrators

SQM Technology, San Diego, CA

Spun off from Physical Dynamics, SQM is a small company with only a few persons devoted to SQUID systems. They have constructed SQUID magnetometers for geophysical research, most often in hostile environments (arctic, underwater, etc.). Current research interests included SQUID NDE. They often use outside vendors (QD, BTi) for major subsystems. Current research support comes from SBIR grants (DARPA, ONR and DoE). Annual revenues are estimated to be less than $1,000,000.

Dynamics Technologies, Torrance, CA

Funded by a DoE SBIR phase II grant, they built a single airborne 6-element system. The magnetometer array consisted of 3 first derivative vertical () gradiometers plus 3 orthogonal magnetometers for electronic noise cancellation) using QD 200 MHz electronics. The probe was constructed by Quantum Design. Gradient sensitivity
~10,000 fT/meter (3 x 10^{-3} g/ft), mostly due to motion-induced noise. Apart from the SBIR grant, annual revenues are minimal (<$100,000).

IBM, Yorktown Heights.

The largest research group devoted to investigation into SQUID devices. The IBM SQUID effort is a basic research activity that started as a result of technical capabilities available in IBM's Josephson computer effort. The Yorktown Heights group has fabricated the world's best SQUID sensors, based on a $Nb/Nb_2O_5/PbAuIn$ edge junction technology. Although these devices are not for sale, IBM has loaned some of them to outside research groups (Helsinki and Cornell). Using a silicon processing line, IBM can fabricate Josephson devices with m, line widths. Linewidths of m may be possible using e-beam techniques. Approximately ten people are involved in the low-T_c effort.
IBM's work on high temperature superconductivity is heavily concentrated on thin-film dc SQUIDs. Their thallium-based high T_c devices have white noise ~10^{-30} Joule/Hz, roughly equivalent to BTi's dc SQUIDs without the use of Dynabias. IBM has successfully combined $YBa_2Cu_3O_{7-d}$ coils with niobium SQUID sensors (operating at 4.2 K) and thallium dc SQUID sensors (operating at 90 K). IBM's effort can be considered to be major and they can be expected to produce a fully functional high-T_c SQUID sensor before the end of 1990. Like the low-T_c effort, approximately ten people are involved in the high-T_c effort.

IBM, Federal Systems, Alexandria VA is the prime contractor on the NCSC, Panama City MADOM refurbishment. Technical support comes from IBM, Yorktown Heights and Quantum Design.

Existing U.S. Capability--Potential Manufacturers

There are several other groups with the ability to produce SQUID devices. For the most part, these groups' capabilities derive from other projects involving Josephson junction research, typically in the area of high speed (digital) electronics.

HYPRES, Elmsford, NY

Manufacturer of Josephson junction based oscilloscopes. HYPRES has the capability to produce niobium and NbN SQUIDs in quantity, and could be considered as a potential foundry operation. HYPRES is funded almost entirely by venture capital groups. Under ONR funding, Hypres has been developing an all thin-film NbN digital SQUID magnetometer. HYPRES has a DARPA/ONR contract to do research into high temperature superconductivity and is working on $YBa_2Cu_3O_{7-d}$ SQUID devices. HYPRES showed early interest into biomagnetism but did not pursue this area due to its capital intensive requirements.

TRW, Redondo Beach, CA

Led by Arnold Silver, TRW has several groups investigating superconducting electronics. Their facilities include Nb and NbN Josephson lines for high speed electronics. For the MADOM program, they bid with CTF Systems on a horizontal dewar. Three contracts support work on high-T_c SQUIDs and several promising techniques for SQUID fabrication are under development. Funding is primarily from DoD (DARPA/ONR, SDIO, etc.). $YBa_2Cu_3O_{7-d}$ rf SQUIDs utilizing engineered microbridges have achieved 1.5×10^{-5} F_0/ at 50 K (f = 100 Hz). $YBa_2Cu_3O_{7-d}$ dc SQUIDs have also been fabricated.

Ball Aerospace, Boulder, CO

Experienced in cryogenics, Ball's main interests are in space-borne applications. Ball is duplicating the BTi 330 rf SQUID electronics for readouts of ultra precise cryogenic thermometers for the Stanford gamma-point satellite experiment. Ball is also supplying the horizontal dewars for the MADOM refurbishment.

Lockheed, Palo Alto, CA

As part of the cryogenics package, Lockheed will space qualify dc SQUID electronics and sensors for the Gravity Probe "B" satellite test of Einstein's General Theory of Relativity.
Hughes Research Laboratories, Malibu, CA
Interests are in high speed electronics. They have been awarded a DARPA contract to do research into high temperature superconductivity.

Rockwell, Anaheim, CA

Interests are in high speed electronics. Rockwell was a bidder on the NCSC, Panama City MADAIR program with assistance from Bill Goree of 2-G Enterprises.
Westinghouse, Pittsburgh, PA
Heavily involved with all aspects of superconductivity, large scale and small scale, both low-T_C and high-T_C. At one time, Westinghouse intended to team with BTi on the NCSC Panama City MADOM program.

RMC Cryosystems, Tucson, AZ

Primarily a manufacturer of cryogenic equipment, RMC sells a Josephson voltage standard system. The Josephson array chip (consisting of 3,020 Josephson junctions) is fabricated by NIST, Boulder. RMC packages and markets the system ($125,000) or appropriate components. Initial sales are expected to be on the order of 11~14/year. Other than Producing superconducting fixed point standards for ultra-low temperature measurements, RMC is not expected to extend its superconducting product line in the near future. RMC has 60 employees with 1989 revenues estimated to be six to seven million dollars.

Sperry Defense Systems Division, St. Paul, MN.

Initial research (ca. 1978) on Josephson junction was for potential computer applications. A Sperry-SHE team was awarded the NCSC/Panama City SQUID MADAIR ASW magnetometer contract in 1980. In 1984, the SQUID magnetometer program was a 24 man effort. By 1984, the cutbacks reduced the effort to 8-10. Technology and product development was mainly supported by government contracts. Sperry published several articles describing the HYBRID SQUID technology developed by S.H.E. Sperry unsuccessfully sought collaboration with Los Alamos National Laboratory to develop a 32 channel system for medical applications with government money. The group was disbanded in 1988.

Conductus, San Jose, CA

Conductus is a small but growing company funded by venture capital, several SBIRs and contracts. The company is led by John Rowell and John Clarke (the latter from Berkeley), and has demonstrated considerable expertise in low-T_C and high-T_C SQUID devices. They also have been developing a high speed superconducting A/D converter together with Hewlett-Packard. Conductus has entered into a CRDA with the Los Alamos P-6 group to supply sensors for developing a ~100 channel SQUID neuromagnetometer. They are a potential manufacturer of MEG and MCG systems, given sufficient capital.

G.E. Medical Systems

General Electric has recently entered the MEG instrumentation arena by entering into collaboration with a company in Italy (Mediterranean Superconducting Sensor Laboratory), related to the Rome group.

University and Government Laboratories

University of California at Berkeley

Most of the top SQUID investigators (Ketchen, Tesche, van Harlingen, etc.) are students from John Clarke's laboratory. This facility was the first to produce a dc SQUID that approached sensitivities of 10^{-34} Joule/Hz. A pioneer in use of SQUIDs for magnetotellurics, his group is now investigating the use of SQUIDs as detectors for low frequency NMR measurements. Clarke's group has had a number of students from the Peoples Republic of China.

Stanford University

The primary interest is in high temperature superconductivity including SQUID sensors. Beasley's group has also successfully produced low noise Nb_3Ge and Nb_3Sn SQUIDs operating as high as 19 K. Measured without input coils attached, the best of these devices had an energy sensitivity better than 10^{-32} Joule/Hz (T = 4.2K, f = 10 kHz). Led by the late Professor William Fairbanks, Stanford University is heavily involved with the use of SQUID magnetometers as readout devices in satellite experiments (zero gravity measurements of the ^4He g-point transition and fundamental tests of Einstein's theory of general relativity — Gravity Probe "B").

University of Illinois

van Harlingen's group in the physics department has produced dc SQUIDs with 10^{-34} Joule/Hz noise levels. These devices, which operate at frequencies as high as a MHz, hold the current record for low noise.

National Institute for Standards and Technology (NIST), Boulder, CO

Formerly the National Bureau of Standards (NBS), the Boulder labs have a sophisticated fabrication facility that is open to foreign visitors. The Italians, in particular, have made use of these facilities to learn how to fabricate the dc SQUID sensors that are being produced at CNR, Rome. As mentioned, NIST supplies the Josephson voltage standard chips to RMC as part of NIST's technology transfer program.
With the advent of high temperature superconductivity, NBS intends to be the "Center for Superconducting Electronics". They have produced a high-T_c ($YBa_2Cu_3O_{7-d}$) break junction rf SQUID that operates at 81 K.

Other

There are several university and government laboratories whose main interest is digital applications (Josephson junctions for high speed electronics). Their facilities and capabilities are directly transferable to SQUID sensors and could easily start production of SQUID sensors if a sufficient reason existed. These include such facilities as the University of Rochester, MIT Lincoln Laboratories and the Naval Research Laboratory (NbN devices). The Jet Propulsion Laboratory has had interest in the past in SQUID magnetometers.

Canadian Capability--Manufacturer

CTF Systems, Port Coquitlam, British Columbia

CTF is a manufacturer of dewars, SQUID sensors, electronics and systems including rock magnetometers (some with cryocoolers attached), geophysical magnetometers and biomedical gradiometers. CTF has supplied 8-element (MADAIR style) gradiometer systems to the Canadian Defence Ministry. They currently offer point-contact niobium SQUIDs, but are developing a thin film dc SQUID.

CTF is working on a 60 channel MEG system that is funded by the Canadian Defence Ministry. The detection coil geometry will most likely be a 3^{rd} derivative axial gradiometer. CTF has a thallium based high-T_c effort (also supported by the Canadian government). A prototype is expected to be finished within a few months with the final design being a year off. CTF is currently seeking funding to support their biomedical development programs. They supplied custom asymmetric dewars and rf SQUIDs for Dornier's dual 14 channel biomagnetometer, along with a dewar, SQUID sensors and electronics for Dornier's hepatic iron stores measurement system. CTF also built the dewar used by the Helsinki group for the Finn's 5 fT/ gradiometer system. Annual revenues from SQUID sales are estimated to be ~$1,500,000.

Europe Capability--Manufacturers

Although the worldwide demand for products incorporating SQUIDs is small (less than 100 units per year), there are several foreign suppliers. Among active commercial manufacturers of SQUID sensors, electronics and systems are:

Cryogenic Consultants, Limited, London, England

CCL is a manufacturer of dewars, superconducting magnets (laboratory and MRI) cryostats, magnetic ore separation systems, SQUID sensors electronics and systems. Systems include rock magnetometers, geophysical magnetometers, SQUID susceptometers and biomedical gradiometers.

CCL offers planar niobium SQUIDs with AlO_x junctions. Their rf SQUID performance is comparable to BTi's (10^{-28} Joule/Hz). Their rf electronics are a duplicate of BTi's electronics. CCL now has available dc SQUID sensors with energy sensitivities better than 10^{-30} Joule/Hz. Their dc electronics have not been described in the open literature. The development of their planar SQUIDs was in conjunction with Professor Lumley of Cambridge University. CCL has delivered some systems with cryocoolers attached to the thermal shields for extended hold times. Estimated annual revenues from SQUID systems is on the order of $1,000,000. CCL's market could be as large as 30+ systems/year by 1992 or as few as ten. This ignores any possible entry by CCL into the biomagnetic market.

Siemens, Germany

Siemens has been involved in SQUID R&D since 1982, most likely for biomedical applications. Like Westinghouse, Siemens is heavily involved with all aspects of superconductivity, large scale and small scale, both low-T_C and high-T_C. Siemens offers a 37 channel (+3 noise channel) biomagnetometer. System sensitivity 5 ~ 10 fT/ with a price of $2,500,000. The first Siemens system in the U.S. will most likely be placed at Stanford University. The sensors are thin film dc SQUIDs (10 on a single wafer) with energy sensitivities of 3.3 x 10^{-31} Joule/Hz above 1 Hz. The system features superconducting connections between an array of SQUIDs on a wafer and a gradiometer array.

Philips GmbH, Germany

A major manufacturer of medical products, Philips has interests in biomagnetism. Their medical instrumentation group at Hamburg has been working with Professors Rogalla and Peters at Twente University. They have developed a 7-channel system that has been used for auditory evoked response measurements. Using 2 cm diameter second order gradiometer coils, its system noise is less than 20 fT/. The SQUID sensors are based on a NbN-MgO-NbN technology with flux noise <10^{-5} F_0/.

Elettronica, S.p.A., Italy

Elettronica is a commercial vendor of rf SQUID gradiometer systems with sensitivities ~30 fT/ (Their early systems used BTi 330X electronics and BMD-5 dewars). Elettronica constructed a 9-channel dc SQUID biomagnetometer system with CNR, Rome. They also have a small developmental cryocooler project.

LETI, France.

A French Government controlled laboratory, Laboratoire d'Electronique et de Technologie de l'Informatique (L.E.T.I.), attached to the Centre d'Etudes Nucleaire de Grenoble (C.E.N.G.) has built rf SQUID sensors and electronics in the past. The LETI group has described thin film dc SQUID. Until recently this group was inactive due to the lack of a sizable market. Because of the intense interest in high-T_C superconductors, L.E.T.I. supplied sensors and electronics to ANVAR, Barras who attempted to construct a SQUID susceptometer.

System Integrators, England

Both Thorn EMI and General Electric Company (GEC) have been building SQUID systems based on commercial SQUID sensors and electronics. Thorn EMI has been supported by the British Ministry of Defence while GEC's interests are medical. GEC has constructed an asymmetric (2^{nd}) gradiometer system, using commercial rf SQUID sensors. They have internally funded a thin film dc SQUID project.

Dornier, Germany

Biomedical interests. Using CTF SQUID sensors, electronics and dewars, Dornier has constructed (under German government funding) a SQUID susceptometer for assessment of hepatic iron stores. They have also built a dual 14 channel biomagnetometer that includes electronic balancing. This system will be used in a magnetically shielded room at ULM University and includes a computer controlled gantry for Probe placement. System sensitivity is thought to be ~20 fT/.

Metronique, France

Manufactures a SQUID susceptometer. The SQUID sensors and electronics are supplied by CCL. Sales are thought to be insignificant.
University and Government Laboratories

Cambridge University, England

Works with CCL in development of thin film SQUIDs.

University of Sussex

Professor Terry Clark developed 430 MHz rf SQUID electronics. Commercially offered (1980) by VG Instruments, only a few sold, less delivered. Clark never allowed design to be frozen and the product was dropped by VG.

Open University, Milton Keynes

Using commercially available SQUID components, they developed a miniature asymmetric SQUID gradiometer with 2 mm dia. detection coil and 5 mm tail separation (dewar supplied by CTF). Intrinsic noise calculated to be 30 fT/. Although intended for biomagnetic investigations, the system would be appropriate for NDE.

Birmingham University

Like NIST (NBS), Boulder, they have constructed a high-T_c SQUID ($YBa_2Cu_3O_{7-d}$) that operates (noisily) at liquid nitrogen temperatures.

Imperial College, London

Using rf SQUID sensors and electronics, they constructed a 7-channel biomagnetometer. System noise level was ~28 fT/.

University of Strathclyde, Scotland

Their main activity is crack detection and NDE. Prof. Donaldson will receive additional funding to work on non-invasive magnetic methods of crack detection (SQUID-based NDE). He was told by the British Ministry of Defense/Navy not to include stainless steel as the Navy was interested in stainless steel. However, Hitachi/Japan is interested in Donaldson's work. Donaldson's group has also constructed a $YBa_2Cu_3O_{7-d}$ rf SQUID that operates at liquid nitrogen temperatures.

The Netherlands

Both Delft and Twente Universities have produced dc SQUID sensors at the 10^{-30} Joule/Hz level. The low temperature group at Twente is constructing a 19-channel systems using first order gradiometer detection coils. The dc SQUIDs are based on a Nb/Al-AlO_x-Nb technology are felt to be of very high quality.

University Karlsruhe, Germany

Has produced excellent SQUID sensors and electronics. They have fabricated first order integral Planar dc SQUIDs and detection coils in conjunction with a novel digital feedback loop. Also active in constructing Nb_3Ge SQUID devices. Prof. Jutzi has developed a digital read-out SQUID with $E_N = 2 \times 10^{-32}$ Joule/Hz. Low frequency noise reduction was achieved using a variant of the BTi Dynabias modulation scheme. Subsequent work on the digital SQUID using single turn input coils has led to field sensitivities of 7.5 fT/ above 6 Hz.

Physikalisch-Technische-Bundesanstalt (PTB), Berlin

A small, capable, well-equipped research group, the PTB is part of the German Commerce Ministry, similar to our NIST (NBS). PTB is exploring promising pre-commercial technologies; their mission is to establish and maintain metrology standards. Guest scientists and industry collaborations are encouraged. Technology developments and assistance are available to German industry. They have a strong program in low temperature physics and technology. PTB has had extensive biomagnetometer activities, and was an early contributor to SQUID technology. PTB also has a submicron microfabrication facility available.
dc SQUIDs fabricated with SAIL (Self-Aligned In-Line) junctions were able to achieve flux noise levels below 10^{-5} F_0/ in locked loop operation. PTB researchers have also constructed a multi-channel magnetometer for magnetocardiography. Using 6.4×10^{-6} F_0/ dc SQUIDs, this system features 37 channels and a noise level of ~5 fT/ above 1 Hz. PTB has fabricated an integral planar dc SQUID 5 x 5 array for biomagnetism, initially for MCG. The PTB has a research cooperation with CNR/Univ. of Rome magnetocardiography group and a collaboration with epilepsy group at Free Univ. Berlin.

Technical University Braunsweig, Germany

Researchers at the Institut fur Hochfrequenztechnik have produced high-T_c SQUIDs with noise level of (6 ~ 7) x 10^{-5} F_0/ with a 1/*f* knee of 5 Hz. A magnetometer was constructed with one of these devices and used to detect the timing signals from an electromechanical clock.

Giessen University, Germany

In the past, they have collaborate with Phillips, Hamburg, along with some interaction with Dornier.

CNR Rome, Italy

Constructed 9-channel gradiometer system with noise levels of 20 fT/. With technology learned at NBS, Boulder, their dc SQUIDs had E_N = 8.5 x 10^{-31} Joule/Hz. The CNR works closely with Elettronica S.p.A. They have a major project to develop new SQUID sensors for imaging neural and cardiac activity among other biomagnetic diagnostic techniques. This has led to a 28-channel neuromagnetometer system. The dc SQUIDs (currently supplied by IBM) connect to 17 axial gradiometers and 11 planar gradiometers. System performance will be announced at the 1990 Applied Superconductivity Conference.

Warsaw Pact

Most groups fall into the University and Government laboratory category. However there are three groups marketing SQUID components and are so designated.

Soviet

The Soviet Union has had a long history of activity in SQUID devices. They are especially strong in the theoretical understanding of the quantum mechanical nature of SQUID devices. A list of references to Soviet activity can be found in the article "Superconductor Electronics: New Prospects" by Likharev. There is also significant Soviet activity in high temperature superconductivity including high-T_c SQUIDs. The Joint Institute for Nuclear Research in Dubna is purported to be manufacturing commercial grade SQUID electronics.

Institute of Radioengineering & Electronics, Moscow

In 1987, the Institute was using a single channel SQUID magnetometer with a noise level of 10 fT/ in an unshielded urban environment. Support equipment include a computer for initial data processing and dynamic image processing. By the middle of 1989, the Institute had constructed a high-Tc SQUID and successfully took MCG (cardiac) data. The SQUID operated at 77 K with a noise level ~5,000 fT/.

Edward Godik, Institute director said (at the 1989 New York Biomagnetism Conference) that the magnetic imaging group has completed their dc SQUID electronics. They are in the process of building a multi-channel system and would like to work with a commercial company on a 50/50 basis. Dr. Matlashov gave the following performance for their dc SQUID: E_N = 5 x 10^{-31} Joule/Hz, L_{input} = 0.6 mH, with the 1/*f* knee at 0.2 Hz. With a detection coil (gradiometer order not mentioned) attached, the intrinsic field noise was 8 fT/ with actual values being 20 fT/. The gradiometer was mechanically balanced to better than 1000 ppm and electronic balancing with an IBM PC/AT (clone) was used to improve rejection of uniform fields to better than 10 ppm. Since then, the Institute has fabricated Nb-AlO_x-Nb dc SQUIDs with flux resolution of ~2×10^{-6} F_0/. Configured as a gradiometer, magnetic field sensitivities of 10 fT/ have been achieved.

Kurchatov Institute of Atomic Energy, Moscow

Their main interest is in MEG. The Kurchatov facility is a new two story wooden building. Inside is an aluminum eddy current (rf) shielded room 5 cm thick. Their magnetometer is an asymmetric first derivative gradiometer. They are using both Zimmerman style two-hole sensors and apparently also have a BTi rf SQUID sensor. They have constructed SQUID sensors of their own design. These devices are were developed in am associated electronics institute (perhaps the Institute of Radioengineering & Electronics in Moscow). Electronic balancing has been used to suppress low frequency noise by 40 dB.

In the past, researchers from the Institute (Ozhogin, Shabonov, etc.) have worked with the 7-channel biomagnetometer system at Helsinki that uses IBM dc SQUIDs. Dr. Shabonov feels all planar devices are the way to go. They participated in aspects of the preliminary design of the Helsinki 24 channel system. Ozhogin has written a Russian language text on biomagnetism and so edits a Soviet journal on high temperature superconductivity.

USSR Academy of Sciences

Kholodov et al (Institute of Higher Nervous Activity and Neurophysiology) describe a dc SQUID magnetometer system with sensitivity of 40 fT/. Other work is described in the proceedings of the 17^{th} International Conference on Low Temperature Physics, Bondarenko *et al.*

Alexandr M. Gorbach (Institute of Higher Nervous Activity & Neurophysiology) has built an optically pumped magnetometer for MCG work. Its sensitivity is 100 picoTesla. He has authored a book (in Russian) on magnetometers. On page 80 is a photo that appears to be that of the BTi model 601 SQUID biomagnetometer that was diverted to the Soviet Union in 1984.

Joint Institute for Nuclear Research, Dubna

The Joint Institute for Nuclear Research, Dubna, USSR constructed a SQUID with noise levels less than 50 mF_0/. They have recently constructed a rf-biased $YBa_2Cu_3O_{7-d}$ SQUID. Operating at 78 K, the energy sensitivity is 9×10^{-28} Joule/Hz, with an equivalent field noise of ~400 fT/ (f > 100 Hz). As a gradiometer consisting of two SQUIDs in opposition (9 cm baseline), its sensitivity is 3,000 fT/meter/ in the white noise region (> 10 Hz). The system has been used for magnetocardiography. The same group has recently developed a single-hole version with outstanding properties. Used for magnetocardiography measurements in a single room, the basic magnetometer has a 1/*f* knee at 1 Hz and an ultimate field sensitivity of ~115 fT/ (equivalent to 3×10^{-4} F_0/). The radio frequency electronics used were "identical to the low-temperature SQUID electronics fabricated commercially by the Physics Facilities Division of the JINR."

Ukrainian Academy of Sciences

Early work in the 1970's by the Physicotechnical Institute for Low Temperatures led to a $<10^{-3}$ F_0/ thin-film SQUID. This Institute has published many papers of SQUID magnetometers, including papers on biomagnetism and geophysical applications.
The Institute of Cybernetics reported on a niobium tunnel junction device with noise levels of 30 mF_0/. More recently, they have constructed a $YBa_2Cu_3O_{7-d}$ high-T_c SQUID operating at 77K with $E_N < 10^{-28}$ Joule/Hz. The Institute is actively promoting its technology to interested parties in view of a potential joint effort in scientific research, manufacturing or marketing. In particular, they describe a high-T_c rf SQUID magnetometer with a magnetic field sensitivity of 400 - 800 fT/ at 77 K. Its intrinsic noise level (0.1 - 150 Hz) is stated to be < 10 fT/ (200 mF_0/). The accompanying dewar claims to have a >30 day hold time. The rf SQUID electronics offer a 120 dB dynamic range. The Institute also offers YBCO powders and precursor materials for sale.

Moscow State University

The department of Physics has been active in constructing SQUID sensors for at least the last five years producing both rf and dc SQUIDs operating at the 10^{-31} Joule/Hz level.

Sektion Physik, Friedrick-Schiller-Universitt Jena — Manufacturer, Germany

The group leader, Professor Albrecht, has more than a decades experience in constructing thin-film tunnel-junction (dc) SQUIDs with noise levels less than 100 mF_0/ (< 60 fT/).
Using a planar dc thin film SQUID with an integrated transformer connected to a second order gradiometer, sensitivities of 20 fT/ have been achieved. The device is a multiloop thin film tunnel junction (Nb-NbO_x-Pb) dc SQUID with an input impedance of 0.7 mH, 3.8×10^{-7} A/F_0 and a flux noise of 1×10^{-5} F_0/. The junction dimensions were 2.6 m x 2.6 m. The latest SQUID sensor from the Jena group, the model "UJ 111" has an energy sensitivity of 2.9×10^{-31}Joule/Hz (2 x 10^{-6} F_0/ into a 0.9 mH input coil). note: these performance figures are comparable with the best dc SQUID commercially available in the West. Their construction is felt to be superior (in terms of reliability) to those supplied to Helsinki by IBM.
Albrecht's group has been supplying most of eastern bloc with niobium and NbN Josephson junctions and is now selling these devices commercially. Customers outside the Warsaw Pact include Helsinki University of Technology, Tampere University and Wurtzberg University. According to Prof. Williamson, the Jena devices have equivalent performances to BTi's dc SQUIDs. These SQUIDs have been used to construct a 5-channel biomagnetometer with mechanical balance of 100 ppm and field noise of 20 fT/.

Czechoslovakia

Czechoslovakian Academy of Sciences, Prague — Potential Manufacturer
The Physics Institute constructed a 440 MHz rf SQUID with a sensitivity of 2.6×10^{-29} Joule/Hz. A review paper by M. Odehnal gives extensive references to work in Warsaw Pact countries.

The Slovak Academy of Sciences have advertised a laboratory rf SQUID system for sale that is comparable to commercially available rf SQUID systems. No customers names are known.
Institute of Physics, Prague
Incorporated SQUIDs into a susceptometer and built a three-axis geophysical magnetometer with a sensitivity better than 100 fT/.

Slovak Academy of Sciences, Bratislava

The Institute of Electrical Engineering, Electro-Physical Research Centre is known to be conducting theoretical, experimental and applied research on the Josephson effect and superconducting electronics.

Poland

Polish Academy of Sciences, Wroclaw, Poland — Potential Manufacturer
Early activity at the Institute of Physics is described in articles in the Review of Scientific Instruments. These devices may be in use in a hospital for biomagnetic applications. The Instytut Niskich Temperatur, has advertised a laboratory rf SQUID system for sale (with a digital fluxcounting accessory). Their early SQUID sensors were based on the S.H.E. Corp. point contact model TSQ SQUID sensor. They have coated a point contact SQUID with NbN, giving the sensor the potential to operate above 10 K.

Finland
Helsinki University of Technology, Helsinki, Finland — Potential Manufacturer

In 1976, Professor Olli Lounasmaa's group constructed 7-channel gradiometer for magnetoencephalography. The system uses IBM dc SQUIDs (supplied by C. Tesche, IBM, Yorktown Heights) with a sensitivity of 5 mF_0/ and extremely low 1/*f* noise. These all thin-film devices are considered to be the world's best. Operating in the Helsinki magnetically shielded room, system performance is 5~6 fT/. The dc SQUID electronics were designed by HUT personnel. With a dynamic range > 100 dB (1 F_0 maximum), the electronics features two ranges and three different slew rates. An impedance damping circuit allow the first derivative coils to operate at full system sensitivity. It should be noted that there has been Soviet access to this system and others in the past.
The Helsinki group (headed by Professor Lounasmaa) completed a 24 channel system in 1989 with Soviet (Drs. Ozhogin and Shabonov of the Kurchatov Institute of Atomic Energy, among others) participated in the early stages of the system design. The 24 channel system uses planar dc SQUIDs (supplied by IBM after Soviet involvement ceased) integrated with planar orthogonal planar first derivative detection coils. It is serving as a test bed for a 100 channel planar gradiometer system. The 100 channel system is intended to be commercially available. At this point, IBM is considering extending their collaboration with the Finns and supplying dc SQUIDs for the first 100 channel system. It is unclear whether or not IBM would be involved in any follow-on systems.
The Finns have the capability to produce their own chips. Their current SQUID chip is a single large wafer with two planar first-order gradiometers oriented perpendicularly to each other

(dB_Z/dx and dB_Z/dy). They were jointly developed by the Finnish State Research Laboratory located on the Helsinki campus) and fabricated to HUT's specification. The Finns claim that SQUID chips are being produced reliably and have noise levels as good as the IBM devices. It should be noted that if the Finnish SQUIDs were as good as IBM's, Helsinki would not need IBM's. The same government agency (established to promote new technology for commercial exploitation by industry in Finland) funded the SQUID development at the State Research Laboratory as well as production of the large number of SQUIDs required for Lounasmaa's 24 channel magnetometer.

The Finnish dc SQUID has the following characteristics:

i) All thin-film improved IBM process: Nb-NbO-Pb/In junctions, lift-off technique, 10 layers.

ii) Process claimed to be reliable, with the ability to produce more than 1,000 devices/year.

iii) SQUID chip designed to be inductively coupled via built-in impedance matching transformer to pickup coil on separate substrate (no superconducting joints), with the detection coils being inductively coupled to the SQUID.

iv) Built-in rf shielding; self-shielded via balanced input coil transformer.

The dc SQUID electronics have a relatively compact, modular design with state-of-the-art performance. Its rfi rejection said to be much better than BTi or any other known design, with minimal noise from transmission lines and matching circuits.

Tampere University, Finland

Experienced in systems integration, Tampere University has constructed a three channel SQUID gradiometer for biomagnetism (cardiography). They have purchased both BTi (rf) and Jena (dc) SQUID components for their work.

Instruments for Technology, Finland

A defunct manufacturer of rf SQUID systems. Technical support came from Professor Lounasmaa's group at Helsinki University.

Neuromag Ltd., the new Finnish venture — Manufacturer

As mentioned, Professor Olli Lounasmaa/Helsinki University of Technology is building a 100 channel planar gradiometer system. IBM is sufficiently interested that (IBM) is considering giving (loaning) Helsinki the SQUIDs for free. The IBM press release in the Wall Street Journal gave the (mistaken) impression that IBM was getting into the MEG business. Lounasmaa has formed a company (believed to be named Neuromag, Ltd. and headed by Dr. Antti Ahonen) to market the 100 channel system. Participants include the Helsinki University group and the Finnish company Instrumentarium. IBM is not listed as a participant in this venture and most likely, the Finns will have to build their own SQUIDs for commercial units. IBM's participation is felt to be to keep IBM's hand in, in case there is a $1 billion market in biomagnetism.

NDRI, Sweden

Although not a manufacturer or designer of SQUID technology, the Swedish National Defense Research Institute is involved in Magnetic Anomaly Detection. Using fixed base rf SQUID systems (single and 3-axis geophysical magnetometer systems purchased from BTi and CTF or constructed by NDRI), they have been able to detect submarines at distances of a few hundred meters.

Asian Capability

Japan

Currently over 75% of SQUID sales within Japan are from U.S. manufacturers (BTi and QD).
Manufacturers

Hoxan

sells laboratory rf SQUID systems and gradiometers for biomagnetism, has not delivered multi-channel biomagnetic system. They are actively marketing their model HSM-2000 SQUID system and have told prospective purchasers that there would be "no problem" in supplying SQUID systems in the PRC. They claim 50 mF_0/ for their thin-film sensor, but this increases to 200 mF_0/ as a system. The equivalent 5 x 10^{-31} Joule/Hz energy sensitivity for the bare sensor sounds far too good for the 18.4 MHz pump frequency used. The electronics appear to be a copy of BTi's 330X electronics. Hoxan has delivered 20+ BTi style SQUID susceptometers in Japan. The susceptometer appear to be a reverse engineered version of the BTi 1st generation model VTS. Hoxan has been developing an integrated SQUID fabrication facility and have developed a dc SQUID, not yet commercially available. Their dewar technology includes the use of carbon-fiber and alumina-fiber reinforced plastics, slitted multi-layer superinsulation and coil-foil thermal shielding.

Shimadzu

Shimadzu sells single channel magnetometer and gradiometer systems along with a 7-channel gradiometer. The probes appeared to be copies of BTi equipment. All systems used rf SQUID technology with system noise = 24 fT/. The electronics also appear to be a copy of BTi's 330X rf electronics.
Shimadzu has built 3-axis geophysical magnetometer (copy of BTi's GMS-45) for Japan Defense Agency, and 8 single channel systems for magnetic monopole experiment for KEK (Japanese High Energy Group).

Yokogawa

Another manufacturer of SQUID components, Yokogawa has delivered 20 rf SQUID systems in Japan. They have also delivered 2 single channel gradiometers for biomedical research (Cardiography and auditory evoked response).

Hitachi

Not yet selling systems, Hitachi is developing a SQUID system for commercial applications. Their major interest is in the commercial biomedical market. Hitachi has not publicly announced their intentions towards the biomedical market, but are rumored to be mounting a major R&D effort. They are also involved with high temperature superconductivity and have made a liquid nitrogen dc SQUID magnetometer (like IBM) with a sensitivity of ~50 picoTesla. The claimed critical current of the actual thin film used to make the SQUID loop is ~6,000 A/cm^2.
Hitachi is also interested in Donaldson's/University of Strathclyde, Scotland NDE work. So much so that Hitachi hired Donaldson's assistant to come to work for Hitachi to look at stainless steel. Hitachi's interest is in corrosion of piping in nuclear reactors. Supposedly Hitachi will collaborate with Donaldson, but Donaldson doesn't expect to get much information back from Hitachi.

Fujitsu

Originally doing Josephson junction research (5^{th} generation computer). Fujitsu has the potential to build dc SQUIDs, but is not presently marketing them. They have announced a planar SQUID on an integrated circuit. The integrated circuit could accommodate >100 devices. The intention is to use these for medical applications. Fujitsu has recently reported on digital SQUID with flux noise of 1 mF_0/.
Fujitsu is rumored to be in a "subconsortium" with other Japanese companies (Hoxan & Yokogawa?) to produce a 200 channel biomagnetometer. Not yet selling systems.

Mitsubishi

Not yet selling systems, Mitsubishi has announced a thin film planar dc SQUID. They have been developing an integrated SQUID fabrication facility. Device sensitivity said to be comparable to commercial dc SQUIDs. Like Hitachi, Mitsubishi can be considered to be a potential competitor for the commercial biomagnetism market.
University, Government and Industrial Laboratories

Aisin

Exhibited (at the 1987 Biomagnetism conference in Tokyo) a Nb_3Ge SQUID (fabricated at Tokyo University) that operates with a cryocooler at T > 10 K. Noise ~200 mF_0/ using BTi 330X (rf) electronics.

TOYO SODA

With researchers at Nagaoka University, TOYO SODA developed a NbN SQUID gradiometer system. The sensor is a planar nanobridge device patterned after IBM dc SQUIDs developed by Mark Ketchen. The SQUID loop is encapsulated in a toroidal structure like current BTi HYBRID dc SQUIDs as described in publications from the now defunct Sperry group. Probe design is similar to BTi single channel gradiometer systems. Sensor flux noise is ~5 mF_0/
(2 x 10^{-31} Joule/Hz).

Nippon Telephone and Telegraph

Although not fabricating SQUID devices, NTT has the capability as they are currently producing Josephson junction gates for digital applications. NTT is interested in SQUID applications, Dr. Ueno having purchased a dual 7-channel Neuromagnetometer from BTi in 1988.

Nippon Electronic Corporation

Like NTT, NEC is producing Josephson junction gates, with the capability to fabricate dc SQUIDs.

ElectroTechnical Laboratory, Tokyo

The ETL has 10 people working on the Josephson junction computer program and 5-6 people working on biomagnetic (neuromagnetism) effort. Funding for ETL is from MITI. Key person at ETL is Dr. Koyanagi. ETL has built a dual channel planar dc SQUID biomagnetometer with integral planar detection coils. Sensitivity 28 fT/ in a magnetically shielded room. The SQUID sensor requires only normal metal connections to room temperature. ETL's intention is to build a 9-channel system. ETL has also constructed a system comprised of three integrated dc SQUID/magnetometer coil devices placed on the orthogonal faces of a cube. A second set of three is located above the first and its output used to (electronically) cancel out uniform fields. System noise (in a shielded room) is better than 30 fT/. ETL researchers have also constructed an integrated NbN dc SQUID magnetometer with MgO barriers. The intention is to couple this particular device with a cryocooler.

Hokkaido University

Interest is in thin film planar gradiometers with NbN and MoN Josephson junctions. These devices have flux sensitivities ~10 mF_0/. Gradiometer designs are fractional loop gradiometers and concentric circles (conceptually similar to (but many orders of magnitude smaller than) those designed by Donaldson/Strathclyde). Shinya Kuriki and colleagues have also developed an ac bias scheme to reduce 1/*f* noise similar to that developed by Simmonds. Hokkaido has also constructed high-T_c SQUIDs.

Osaka University

Developed 6-channel rf SQUID gradiometer for MCG work. 3 (second gradient) orthogonal channels are for detection of MCG, the other 3 (magnetometer) channels are for electronic noise cancellation. Osaka is developing rf and dc SQUID electronics for multi-channel SQUID systems.

Tokyo University

developed Nb_3Ge Dayem bridge SQUID sensor. The sensor noise was below 200 mF_0/ using BTi 330X (rf) electronics. Tokyo University supplied the sensor to Aisin for use with a closed cycle refrigerator.

Kyushu University

Developing an all-planar (Nb-NbO-Pb/In) dc SQUID gradiometer with design goals of 7 mF_0/ and gradient sensitivity of 24 fT/cm/.

Nagoya University

NbN microbridge dc SQUID development has led to devices with flux noises less than 50 mF_0/. Researchers from Aisin have joined this effort.

Nagaoka University

Another group working on NbN dc SQUIDs, they have measured flux noises of 30 mF_0/. Intrinsic noise is felt to be three times lower.
Institute of Physical and Chemical Research
The Institute works with Shimadzu Corporation on a dc SQUID development program.
Research Development Corporation of Japan (JRDC)
Yet another dc SQUID development program, the aim is to produce magnetometers.

Taiwan

National Taiwan University
Working on Josephson junction characteristics. Also has high T_c interests.

China (PRC)

Research on SQUID devices is being performed at a number of institutions including Nanjing and Beijing Universities. Activity has included both high-T_c and low-T_c devices. As mentioned earlier, a significant number of Chinese researchers have trained in the United States. Additionally, a number of SQUID systems have been acquired from COCOM countries for basic and applied research. Specific activity of interest includes:
National Institute of Metrology
S. Q. Xue and colleagues have produced a thin-film Nb-Si-Nb tunnel junction with an energy noise of 2 x 10^{-28} Joule/Hz.
Harbin Nuclear Instrument Factory
Under the supervision of the China Metrological Scientific Research Institute, they manufacture the model SQD-1 rf SQUID system. Biased at 30 MHz, it has a flux noise of 200 mF_0/.
Electronics features are similar to BTi's model 330X electronics.

India

National Physical Laboratory, New Delhi
One of many groups in India working on high temperature superconductivity, they have fabricated a high-T_c rf SQUID with flux noise ~2 x 10^{-4} F_0/.

South America

Research programs (mainly in biomagnetism) exist at Pontificia Universidade Catolica, Rio de Janeiro, Brazil and the Instituto do Coraao in Sao Paulo, Brazil among others. Budgets normally do not permit purchase of commercially available systems. Components are purchased and systems built in various laboratories.

Africa

Both Israel and South Africa have purchased laboratory SQUID systems for scientific research, but are not known to be involved in the development of SQUID devices.