

A comparison of the recognition of fearful facial stimuli in a population with medically intractable temporal lobe seizures before and after surgical intervention

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A. Study Purpose and Rationale

a. Overview

By mapping changes in brain hemodynamics associated with specific tasks, functional MRI allows the localization of human mental operations related to specific activities. When the brain's neuronal activity increases, blood flow to the active area increases proportionally, while the oxygen consumption in that area does not increase at the same magnitude, creating an area with decreased deoxyhemoglobin (Fox, et al, 1985). Taking advantage of the fact that deoxyhemoglobin is paramagnetic, it serves as an endogenous contrast agent in T2* weighted MRI signals (Ogawa, et al, 1990 a and b). Thus, areas with high neuronal activity and concomitant increased blood delivery with lower deoxyhemoglobin levels, can be observed with a resolution of approximately 1.5 x 1.5 nlm.

The amygdala elaborates and expresses autonomic and behavioral responses to emotionally relevant stimuli (Adolphs et al, 1999; Young et al, 1995, Calder et al, 1996). Functional imaging studies in humans have demonstrated the amygdala to participate in facial expression processing. Lesion studies revealed the importance of the amygdala and related structures of the anterior and medial temporal lobes in the recognition of emotions from visual stimuli. Also, evidence exists that patients with bilateral amygdala damage typically fail to recognize facial expressions, with fear recognition being most severely affected (Adolphs et al, 1994; Adolphs et al, 1999; Young et al, 1995, Calder et al, 1996; Broks et al, 1998).

Patients with temporal lobe epilepsy (TLE) often incur damage to the amygdala complex and hippocampus, with mesial temporal sclerosis (MTS) the most common neuropathological finding in mesial temporal lobe epilepsy (MTLE). MTS is often associated with early childhood febrile seizures and subsequent drug-resistant seizures of adolescence. Prolonged febrile seizures of childhood have been associated with severe amygdalar damage (Cendes et al, 1993 a). In vivo volumetric measurements in NITLE patients revealed a ten to thirty percent amygdalar volume reduction, with neural loss and prominent gliosis reported in many histopathological studies (Bronen et al, 1995; Cendes et al, 1993 a and b; Gloor et al, 1992; Saukkonen et al, 1994). MTS describes neuronal loss and gliosis of the hippocampus, entorhinal cortex, and amygdala complex. Isolated amygdala damage occurs in approximately 10% of patients with TLE (Hudson et al, 1993; Zentner et al, 1999). Patients with drug-resistant TLE are often evaluated neuropsychologically via tasks assessing language, memory, visuospatial, and executive abilities (Adolphs et al, 1995; Anderson et al, 2000; Rapcsak et al, 2000; Adolphs et al, 2001). Selective damage to the human amygdala is extremely rare, but partial unilateral damage to the amygdala and surrounding structures is typical following neurosurgical temporal lobectomy, the most common surgical procedure in the treatment of medically intractable epilepsy (Adolphs et al, 2001). Emotion recognition studies in patients with unilateral temporal lobectomies for epilepsy have yielded conflicting results (Adolphs et al, 1995; Anderson et al, 2000; Rapcsak et al, 2000; Adolphs et al, 2001). Patients with right-sided NITS, as compared to left-sided NITS or other temporal or extratemporal seizure loci, were impaired in emotion recognition. Also, subjects with right-sided MTS demonstrated maximum impairment in the recognition of fear, and lesser impairment of sadness and disgust recognition. In addition, the presence of febrile convulsions and early onset seizures (onset before age five) strongly correlates with the severity of emotion recognition impairment. Surprisingly, the results demonstrated that patients with right-sided MTS and drug-resistant epilepsy may be impaired in the

recognition of emotions from facial expressions before lobectomy for epilepsy treatment. Conversely, one study reported that certain subjects with unilateral right amygdalar lesions exhibited no emotion recognition impairment in any emotional category (Meletti et al, 2003).

These studies' results raise the possibility that there may be a critical period of life that exists for establishing the neural network that underlies this ability to recognize facial expression. The results implicate that early insult to the right mesiotemporal structures may be crucial to cause emotion recognition deficits, while damage (structural or functional) that occurs later in life (seizure onset after five years of life) results in no deficit. This data contrasts the notion that early damage could allow plastic compensation of a lesioned function; rather it suggests that if the right anteromedial temporal lobe network is disrupted by epileptic activity in early childhood, physiologic phenomena of plastic reorganization is prevented (Meletti et al, 2003). Epilepsy affects the brain's ability to undergo functional reorganization (Chugani et al, 1996). Thus, there may be a critical period in early childhood where interictal/ictal seizure activity involving the right temporal lobe may affect the development of emotion recognition ability. It seems unlikely that the deficit in fear recognition merely reflects an enhanced difficulty in decoding fearful faces, as basic visuoperceptual abilities with face stimuli appeared to be unimpaired in patients with right-sided MTS (correct execution of the Benton Facial Recognition task, where patients match the faces of identical individuals taken under different views and lighting conditions to provide a sensitive measure of basic visuoperceptual function) (Adolphs et al, 2001; Meletti et al, 2003). The right medial temporal lobe modulates fear responses when viewing emotional pictures (exposure to visual information), a finding consistent with emotional processing being ascribed to the right hemisphere. The left medial temporal lobe modulates fear responses when those responses are the result of a linguistic/cognitive representation acquired through language, which like most other verbally acquired material often involves the left hemisphere (Funayama et al, 2001).

Another study found a modest negative correlation between the extent of amygdalar damage and facial emotion recognition performance, consistent with previous studies that have provided clear evidence for the amygdala's role in this regard. Despite this general consensus, however, examples of patients with complete bilateral amygdala damage without any impaired recognition of facial emotion exist (Adolphs et al, 1999; Hamann et al, 1996). Also, patients with complete right unilateral amygdala damage who have no difficulty with emotion recognition tasks have been described, whereas other patients with minimal amygdala damage have been noted to be severely impaired in emotion recognition tasks (Adolphs et al, 2001). A recent study investigated neural responses to threat associated with the conscious and unconscious perception of fearful faces in normal subjects who varied in their sensitivity to threat, as measured by Spielberger's State-Trait Anxiety Inventory (Spielberger et al, 1970). The study delineated that unconscious emotional processing modulated activity only in the right basolateral aspect of the amygdala, while conscious emotional processing modulated activity only in the right dorsal central nucleus. Activation of the dorsal amygdala by conscious threat was independent of trait anxiety, while the basolateral's activity to unconscious threat was predicted by individual trait anxiety measures (Etkin et al, 2004).

b. Specific Aims

There have been no studies, to-date, that have compared recognition of fearful facial stimuli in a population with medically intractable temporal lobe seizures before and after surgical intervention. This prospective case-control study will subject patients to the same facial recognition tasks before and three months following surgical temporal lobectomy to determine if a difference in the patients' recognition of fearful stimuli is observed. In addition, specific areas of activation when viewing fearful stimuli will be examined in patients and controls to see if the right amygdala is, in fact, activated. The imaging studies will examine for left compensatory amygdala activation or other areas within the brain that may be active in patients with temporal lobe seizures or status post surgical intervention. Of particular interest will be to compare the fear responses in late-onset (>5 years of age) temporal lobe epilepsy patients with early-onset (<5 years of age) patients. Why does the majority of right-sided early-onset MTS patients exhibit impaired facial recognition testing, while those with left-sided early-onset MTS or late-onset temporal

epilepsy do not exhibit these deficits. Is there a left sided compensation in lateonset right-sided MTS patients to maintain emotional facial recognition? Is there any ability to process fearful stimuli in some of the early-onset right-sided MTS patients and does this altered function recede after lobectomy? As right basolateral activity to unconscious threat stimuli was shown to be predicted by individual trait anxiety levels, this study may reveal decreased anxiety levels following right temporal lobectomy. From the information gained by this study, testing recognition of facial emotion might become a useful part of the extensive clinical and neuropsychological evaluation of patients with epilepsy. This study will hopefully reveal a precise structural -functional association in the right anteromedial temporal lobe.

c. Significance

One objective of this study is to develop specific tasks that elicit specific activity in specific regions of the brain and then localize these activated brain regions via functional magnetic resonance imaging, fMRI. Possible benefit to neurosurgical planning for individual tumor or seizure resections is one obvious aim in this study, but so too is further delineating functional organization of the human cortex when exposed to visually engaging fearful stimuli.

B. Study Design and Statistical Analysis

a. Study Groups

Based on neurophysiologic and MRI findings, patients suffering from drug-resistant epilepsy who have been recommended for temporal lobe epilepsy surgery by this university's neurology/neurosurgery departments will be selected for study. Noninvasive neurophysiological evaluation via interictal EEG recordings and prolonged video-EEG monitoring to record the patients seizures, in conjunction with clinical features of the seizures, and MRI imaging will be used to define cerebral structures involved in the epileptic activity. Inclusion criteria will be evidence of medial temporal sclerosis, agreement between the noninvasive neurophysiologic data and MRI findings defining the side and lobe of the epileptogenic area, and no history of psychiatric illness as these pharmacologic drugs may adversely affect neural processing. Antiepileptic medication should be continued during the imaging period. Often times, antiepileptic medications are continued, unchanged, for at least the three months following surgery, so these drugs should not represent a variable in the study. NMI will be used to investigate the temporal lobe structures in detail. The presence of MTS will be evaluated qualitatively by visual inspection on NMI as atrophy in T1-weighted sequences and increased mesial temporal signal intensity (T2-weighted and fluid-attenuated inversion recovery sequences) are considered markers for MTS (Meletti, 2003). Further, after the temporal lobectomy, the temporal lobe region will be evaluated by neuropathologists to quantify gliosis, as WS evaluation via imaging studies is imprecise. The patients undergoing temporal lobectomy will range in age from 18-75 and be subdivided into four groups-1) early onset (before age 5) with right sided temporal lobe epilepsy, 2) early onset (before age 5) with left sided temporal lobe epilepsy, 3) late onset (after age 5) with right sided temporal lobe epilepsy, and 4) late onset (after age 5) with left sided temporal lobe epilepsy. Controls will be comprised of healthy volunteers with no history of epilepsy, neurologic or psychiatric illness, aged 18-75. Controls and patient groups will be matched for age, sex, and education level.

There will be approximately eight to ten people in the control group and eight to ten per subdivision of the temporal lobectomy patients. Each non-impaired volunteer will be matched by gender, age, and education level with an epileptic patient. These numbers were derived using sample size equations assuming a power of 90%, an alpha of 0.05, a required effect size of 7% and a standard deviation of 5% (based on pilot data done by Dr. Joy Hirsch). Data from each subdivision of patients will be compared with controls. In addition, these subdivisions can be grouped and compared against each other and the controls for the chosen number of subjects allows for multiple comparisons.

This study will be of the same design as the fMRI studies currently ongoing in the fMRI lab, under the IRB protocol, "Functional Mapping of the Human Brain Using NMI: Development of Techniques and Methods", written by Dr. Joy Hirsch. "Baseline" scans will be obtained where the subject

is doing nothing but looking at alternating plus and minus signs and pressing the response pad when they see a star and "active" scans when the subject is observing a fearful stimuli. Each of the tasks will compose a separate run.

Image data are stored off-line in the fMRI image analysis computer. The fundamental unit of analysis is the single voxel, where signal intensities are compared over all acquired images. A control period is imbedded in the image acquisition sequence by using flanking baseline time periods between epochs. Voxels are sorted into two categories, activated and non-activated, based on the decision rule-if the baseline and stimulation means are statistically different, then the pixel is identified as activated. If the pixel is deemed non-activated, it is excluded from further consideration. If the voxel is identified as active, it is assigned a color code based on the certainty of its activation (p-level) and the polarity of activation (more or less active than baseline scans). Average signal level acquired during each run will be compared to the average signal level of the stimulation images using independent t-tests (Winer, 1971).

It is assumed that multiple sources can lead to voxel activation-chance, motion, including pulsatile movements of the brain, gross movements of the head, and the flow of CSF, and the BOLD (Blood Oxygen Level Dependent) signal (Bandettini et al, 1993). To isolate the subset of voxels with activations due to BOLD response, previous researchers have assumed, additionally, that the anatomical "motion and chance" voxels tend to vary over repeated epochs. Corresponding anatomical slices from repeated epochs are registered based on the anatomical features, and those color coded voxels that are coincident in all epochs are stored, while all others are excluded from further consideration. As the same slices will be taken on each image acquisition run, the anatomies are easily registered and the coincidences in voxels that occurred in the three time frames identified. Only those voxels identified as coincident during the three epochs will be used in the group analysis.

Areas of significant activation in response to viewing fearful stimuli will be analyzed from each individual. All data from epileptic patients will be compared to the compiled data from the normal volunteers for each run using t-tests. Images will be motion corrected and spatially normalized to a standardized template and spatially smoothed. Various image registration and "warping" techniques will be applied to compare images within the database, to ensure appropriate anatomical areas of various individuals' brains are being compared. Data will be analyzed and displayed using SPM2. The results will be displayed in two- or three-dimensional formats individually and over the entire sample of patients and normal volunteers.

All estimates of error rates (false positives) are based on empirical determinations from images acquired on copper-sulfate phantoms that simulate brain intensities in order to avoid potential errors due to either non-independent samples or repeated t-tests. A copper sulfate ball is scanned and regional flow monitored. As this ball should have no regional flow, any flow registered by the scanner will be considered a false positive result and the scanner will be recalibrated.

C. Study Procedures

a. Imaging Procedures

Images will be acquired on a 1.5T General Electric Twin Speed magnetic resonance scanner using a gradient-echo T2*-weighted echoplanar imaging (EPI) with blood oxygen level dependent (BOLD) contrast pulse sequence. A 40 x 20 cm field of view imaged on a 256x128 grid yielding an in-plane resolution of 1.56 x 1.56mm and slice thickness of 5 mm or less is typical. On each run, simultaneous images will be acquired on multiple contiguous slices chosen to cover either the entire brain or the region targeted as the most likely focus of task-related activity. Slice positions are based on a conventional "scout" image obtained prior to the run usually using a three dimensional T1-weighted spoiled gradient recalled (SPGRS) sequence. Slice positions will be maintained as constant as possible from run to run in the case of repeated scans. All experiments will be run either in pairs or in a grouped manner to take advantage of the coincidence options for image -processing.

b. Experimental Procedure

Prior to entering the scanner room, all subjects will have given written consent to participate in the research study. A form modeled on the non-patient volunteer consent form as currently used in the fMRI lab under Dr. Joy Hirsch's Study Protocol #14371. Participants will sign a HIPAA Clinical Research Authorization form and complete a handedness questionnaire. Then, the subjects will be screened for safety factors using a standardized form in the fMRI lab. The list of contraindications will be reviewed with the subject by the consenting investigator and also by the NIR technician who is responsible for the safety of subjects while in the scanner.

Next, the subject will enter the scanner room. In addition to safety, every effort is made to ensure the subject's comfort. The subject will be positioned on the platform of the scanner in the same manner as in a conventional clinical scan using a standard coil and cushions to stabilize the head. Earplugs are provided to reduce scanner noise. The subject will wear goggles that correct for vision as no glasses are permitted in the scanner. Conventional MR images (T1) will be acquired at the start of each session to locate plane lines and anatomical features, enabling investigators to ensure proper placement of the subject. Next the subject will be shown an alternating plus and minus sign and asked if they are able to see the object and whether it is in focus. This identification task will ensure that the subject can see the screen adequately and that appropriate corrections for visual acuity have been addressed. A practice run will occur so that the patient can become familiarized with the finger touch pad.

At this point, the actual recorded scanning will begin. The patient will be asked to focus on a screen with a central plus signal for an initial baseline period of fifty-two seconds.

As each image of the brain takes four seconds to acquire, thirteen images of the brain will be obtained during this baseline. Often, the first three images are discarded, so ten comparison images spanning the entire brain will be used. Then, sensory-motor finger tapping and flashing checkerboard will be shown to the patient so that the language center is appreciated and well-known areas of brain activation can be observed to ensure that the antiepileptic drugs that the patient is taking do not interfere with the results (neurovascular coupling). This aspect will take approximately two minutes. The patient will rest for forty seconds and then begin with the color identification task. For the color identification task, activity in the amygdala will be examined during conscious and unconscious presentations of threat stimuli. A subtractive approach is used and the conscious perception of threat is deemed a non-masked threat, while the unconscious perception of threat is a masked threat. The presented faces are artificially colorized red, yellow, or blue. Each stimulus presentation involves instructing patients to stare at the center of the screen. Then, a face is presented for 200msec. Within 1200msec, subjects have to press the key pad, corresponding to the color of the face presented. Non-masked stimuli consist of 200msec of a fearful or neutral expression, while the backward masked stimuli consist of 33msec of a fearful or neutral face, followed by 167msec of a neutral face mask belonging to a different individual, but possessing the same color. Prior to the functional run, patients will be trained in the color identification task using unrelated neutral face stimuli that are cropped and colorized as the non-masked faces will be. The functional run will be started once patients can identify colors accurately in the practice run, in order to avoid learning effects. This trial will have patients exclusively identify color of faces. After the functional run, patients will be told that there were fearful faces presented and will be shown the stimuli again, and asked to indicate whether fearful faces were seen on the masked epochs. Patients who report seeing fearful faces will not be included for analysis (Etkin et al, 2004). Forty faces will be presented, so a trial will take 56 seconds. The patient will rest for forty seconds after completing the trial, and then another active period for fifty six seconds will occur, followed by forty seconds of rest.

Then, the emotional recognition test will run for 200 seconds including a rest of forty seconds. To study the facial recognition of fear, much of the experimental design will mimic previous researchers' designs. For the experimental task, black and white pictures of male and female faces demonstrating fearful and neutral facial expressions will be chosen from the Ekman and Friesen standardized series. The faces will be cropped to eliminate background, hair and jewelry cues, and oriented to maximize inter-stimulus alignment of eyes and mouths. Pictures of neutral and fearful faces will be shown and

patients will match the displayed facial expression with the corresponding verbal label and demarcate this choice with the finger key-pad. The emotional recognition test will occur with forty images of neutral or fearful expressions displayed for one second each and then the patient depresses the finger pad within one second to signal the appropriate expression. A rest period will then occur for forty seconds, followed by a second eighty second active period, and then another forty second rest. To control for subject's basic visuo-perceptual ability with facial stimuli, a face-matching task will be employed. Again, using the Ekman and Friesen series, a vertical column of two faces with neutral expression will be displayed and the patient will need to select the photograph that matches the stimulus face. Distracters will be photographs of different people of the same sex. Fifteen sets will be presented for three seconds each. Thus, each active round will be forty five seconds and will be followed by a forty second rest. With two active trials and one rest period, this component will last one hundred and thirty seconds. Following the experiments, a high-resolution fMRI will occur for twelve minutes. Thus, it is estimated that subjects will be inside within the fMRI machine for approximately twenty-seven minutes.

Once the patients emerge from the fMRI, more substantial facial emotional recognition testing and face matching testing will occur. Again, for the facial emotion recognition task, pictures of facial affect, from the Ekman and Friesen series, will be shown and patients will match a displayed facial expression with a verbal label for one of the following five basic emotions-happiness, sadness, fear, disgust, or anger. Five face stimuli will be used for each emotion, giving a total of twenty five trials. As both controls' and neurologic patients' most frequent recognition error occurs when differentiating between fear and surprise, faces with surprised expressions and the corresponding verbal label will not be used (Rapcsak et al, 2000; Ekman et al, 1976). To test this emotion recognition, pictures will be presented one by one. Verbal labels for the five facial expressions will be printed under each picture and the subject will need to select the word that best describes the emotion shown in each photograph. The face matching task will again be used. Using the Ekman and Friesen series, a vertical column of four faces with neutral expression will be displayed and the patient will select the photograph of the stimulus face. Distracters will be photographs of different people of the same sex. Twenty-five trials will be conducted. Upon completion of these two tests, the Spielberger State-Trait Anxiety Inventory test will be administered.

As the brain can be scanned in forty seconds, each experiment will yield approximately forty entire brain scans. Performance will be assessed via a standard push-button technique, enabling calculation of the percentage of correct responses for each individual during each run. The rest periods that surround the active periods will be used for baseline comparison for each individual for each task. This experimental design will be performed on controls once, but twice on patients with MTS-1) before their temporal lobectomy and 2) three months after their surgical procedure, ensuring that antiepileptic drug dosing has not changed.

c. After-Scan Interview

Following the imaging session, the investigator (or designated co-worker) will ask the subject to report their experience. These discussions are aimed at confirming that stimuli were seen as expected and that responses were provided according to instructions. Questions regarding the experience will be answered at this time.

D. Study Drugs

None.

E. Medical Devices

All equipment is FDA approved for clinical MR scanning and commercially available. The scanner used in this experiment is only used for research purposes.

F. Study Questionnaires

All subjects are asked to fill out the Biographical Information and Edinburgh Handedness inventory prior to the scanning procedure. This is a standard twelve question form that is intended to document hand dominance and serves to collect biographical information: gender, age, and ethnic information-as recommended by Federal Guidelines. All subjects are also required to fill out the Screening Questionnaire to confirm eligibility for scanning based safety-related factors. No other questionnaires are anticipated, but if necessary later, these will be submitted for IRB approval.

G. Study Subjects

a. Eligibility Criteria (Normal Controls)

Volunteers will be recruited from a pool of students, interested colleagues, and investigators involved in the projects. The eligibility criteria for normal volunteers include all individuals between the ages of 18 and 75 who are without neurological complaint and who are not currently receiving treatment for a neurological disorder. Subjects must have no history of brain injury. All safety criteria (as determined by screening questionnaire in laboratory) must be met and any woman who suspects she may be pregnant or is confirmed pregnant will not be scanned. In accordance with all Federal guidelines, women and minorities are expected to be represented according to their distributions in the subject population.

b. Eligibility Criteria (Patients)

Eligibility criteria for medically intractable temporal lobe epilepsy patients include all individuals between the ages of 18 and 75. Relevant clinical information such as age, diagnosis, and handedness will be recorded in addition to the findings on conventional anatomical and functional localization procedures performed as part of a routine clinical evaluation. These techniques include PET studies, electrophysiological studies such as EEG, neurological examinations, neuropsychological evaluations, results on intra-cortical stimulation performed during surgery, and post-surgical outcome as assessed by physical examination. After the surgical procedure, the patient will partake in a second fMRI study that is identical to the pre-surgical study for comparison with the pre-surgical results. All safety criteria (as determined by screening questionnaire in laboratory) must be met and any woman who suspects she may be pregnant or is confirmed pregnant will not be scanned. In accordance with all Federal guidelines, women and minorities are expected to be represented according to their distributions in the subject population.

H. Recruitment of Subjects

a. Healthy Volunteers

Laboratory practice is to keep a list of those people who contact the lab to volunteer for a functional study. Word-of-mouth and educational benefit fill the need for most volunteers. Volunteers are called from the list on an "as needed" basis. In cases where the volunteer waiting list is not sufficient, a recruiting advertisement will be drafted and submitted for IRB approval. It is based on a similar one from Memorial Sloan-Kettering Cancer Center. One group of potential healthy volunteers who will not be recruited is employees in the functional MRI Center at Columbia or any person directly employed by any principal investigator. Although employees may be subjects if they wish, their participation is in no way related to their employment and their participation is not solicited.

b. Temporal Lobe Epilepsy Volunteers

All patients who will be offered the opportunity to participate in the proposed study will have been identified by their attending physician (Departments of Neurology and Neurological Surgery at CPMC) and referred to our research personnel. A member of the research team will explain the study to

the patient, and if he/she agrees to participate, written consent will be obtained. Patients who have received conventional functional localization studies will be informed that those results will be compared to the fMRI results. After the therapeutic surgery, the patient will partake in a follow-up fMRI procedure three months following the surgery. Subjects will be provided with a signed copy of the consent form.

Informed Consent The key elements of the informed consent procedure which will be explained to the subjects are: 1) The research status of the study 2) The prospect of physical and psychological risk and the provisions for it 3) The lack of guarantee of benefit from participation 4) The confidentiality of the subjects' results 5) The voluntary nature of the study 6) The lack of consequence to medical care of the decision to consent or refuse to participate 7) The freedom to withdraw from the study at any time 8) In healthy volunteers, the possibility of an incidental finding based on the anatomical scan

I. Confidentiality of Study Data

Research and hospital records are confidential. Subject and patient names or any other personally identifying information will not be used in reports or publications resulting from the study. The Food and Drug Administration or other authorized agencies may inspect the records. All records related to involvement in this study will be coded to insure privacy. The University's compliance with HIPAA regulations will be explained and all study subjects will sign the HIPAA clinical research authorization form.

J. Potential Conflict of Interest

No investigator in this study has any financial or proprietary interest in a procedure under investigation or any potential financial benefit from results of this study.

K. Location of the Study

The MR scanner is the 1.5T GE Twin Speed located in the basement of the Neurological Institute, as part of the functional NMI center. All required image analysis capabilities will be available on the dedicated fMRI analysis computer in the laboratory.

L. Potential Risks

There are no known risks associated with procedures used in this study. It is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized by protective ear devices, a mirror on the head coil that enables a view outside the scanner, and experienced technicians who will monitor all subjects for distress and reassure patients when necessary. In the event that a patient becomes anxious during a scan, the study will be halted. Patients will be able to communicate with the investigators at all times using the intercom system should they wish to request that a study be terminated or have concerns or questions during the procedure. The subject is in full view of the operator at all times.

For healthy volunteers, the probability of an incidental finding that might lead to diagnosis of an unknown abnormality is greater than zero. All subjects will be alerted to this possibility during the consent process. All subjects will be provided copies of their anatomical scans and advised to see a physician for further evaluation if they have concerns.

M. Potential Benefits

Study participants will contribute to the study of human brain mapping. Subjects are offered the opportunity to review results with the investigators in an effort to provide an educational advantage. Volunteers are also provided copies of their anatomical scans for reference. Other benefits include

contributing to the understanding of the functional organization of the human brain. Although, it is hoped this research study will be of benefit to the subjects and patients and that it will help others, it is unknown if it will help any individual directly. Participation in the study, however, will provide information which will increase investigators' knowledge of how the human brain is functionally organized, and will thereby contribute to a better understanding of the brain, as well as contribute to the development of novel applications for clinical diagnosis and treatment.

N. Alternative Therapies

This study will not provide a specific therapy. The alternative to participation is nonparticipation in the study.

O. Compensation to Subjects

If a subject is injured as a result of participation in this research study, emergency care, hospitalization, and outpatient care will be made available by the hospital and billed to the patient or subject as medical expenses. No money will be provided by the hospital as compensation for a research-related injury.

P. Cost to Subjects

None.

Q. Minors as Research Subjects

None.

R. Radiation or Radioactive Substance

None.

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