Routine Functional Magnetic Resonance Imaging of the Brain (HUM00093760)

Master Protocol

Objective

The objective of the studies conducted under this protocol is to image brain structure and brain activity in response to external stimuli using magnetic resonance imaging.

The specific aims and hypotheses of these studies will vary from study to study, but in general we aim to use magnetic resonance imaging to

1- measure physical features of the brain in our research participants.

2 - identify active regions in the brain responsible for specific cognitive processes.

3 - identify brain circuits and connectivity between brain regions.

Background Information

Functional MRI is a very powerful tool for cognitive neuroscience. It allows investigators to obtain images of the brain that reflect the underlying level of activity in the neuronal tissue. MRI images, in general, are obtained by a placing the subject inside a large magnetic field and applying a number of carefully designed combinations of additional magnetic fields and radio waves. The signal intensity observed from tissue in an MRI is a function of the physical properties of the tissue in combination with the timing and characteristics of these magnetic field pulses and radio waves. Some of the physical properties of the tissue that affect the MRI image are blood flow and the presence of oxygenated blood, which change during brain activity. As a result, functional MRI allows us to observe neuronal activity by observing the changes in blood flow and oxygenation that take place when neurons are active. The main advantage of MRI technology is that we can obtain both structural information and information about the brain's activity by using different combinations of imaging parameters. MRI does not require any invasive procedures or the injection of contrast agents for these purposes.

There is an extensive amount of information in the literature regarding functional MRI. It is currently widely used as a tool of cognitive psychology and neuroscience. Literally, thousands of research papers have been written based on FMRI data. The UM FMRI laboratory began

scanning human participants for these purposes in 1999 and has made a significant contribution in this regard. This technology continues to provide insights into the human brain non-invasively, and with exquisite detail that would not be available otherwise.

Most functional MRI studies involve using an MRI scanner to estimate neural activity while participants lie in the scanner and perform a behavioral task. In the vast majority of cases, there is a relatively clear division between the behavioral task and the scanning. The behavioral tasks are very much like the standard behavioral experiments that IRB-HSBS reviews every day. For example, participants might view visual stimuli projected on a screen and then make responses based on those stimuli by pressing buttons with their fingers. Many other variants are possible (presenting auditory or tactile stimuli, requiring vocal responses, etc.). The behavioral component of many of these studies involves extremely low-risk procedures that would likely be eligible for expedited review by IRB-HSBS. Currently, all fMRI studies are reviewed by the IRBMED boards. We propose that a single, companion IRBMED application cover the standard scanning protocols that are routinely used across different studies that can be used with approved IRB-HSBS studies that involve a routine fMRI component.

IRB-HSBS researchers must obtain approval for the specific research study, and that the fMRI lab personnel will verify the approval, prior to any fMRI activity taking place.

Methodology

The specific designs of the neuroscience experiments (stimulation protocols, etc) will vary depending on the investigators and will undergo a separate review by the Behavioral Sciences IRB. The standard fMRI protocol is minimal risk as presented and applies only to IRB-HSBS research protocols with healthy adult subjects. The procedures described in this protocol are limited to the MRI scanning, as follows.

We will perform "routine" scans. For the purposes of this companion protocol, routine is defined as:

- No contrast agents (e.g., gadolinium) may be utilized.

- The MRI pulse sequences will not use gradients that exceed 120 mT/m/s or RF pulses that exceed 1 Watt/Kg.
- The study may not involve any drugs or other medical interventions.
- Patients may not be included as subjects in the specific study sample.
- The participant's medical records may not be included as part of the study protocol.
- The study may not utilize transcranial magnetic stimulation (TMS) or other external methods of disrupting brain function.

Studies involving patients, a contrast agent, a medical intervention, or a non-standard scanning protocol, or studies utilizing transcranial magnetic stimulation or other external method of disrupting brain function are not eligible under this companion study approval.

Preparation: The participants will be prescreened for inclusion and exclusion criteria according to the particular study. Subjects arrive at University of Michigan Functional MRI Laboratory. The consent form is reviewed and the experiment explained. Contraindications for an MR scan are reviewed with the subject orally, and a form is completed and reviewed to ensure the absence of any contra-indications. The subject is instructed to remove from their person all metallic objects, jewelry, belts with buckles, wallets, ID cards. Personal possessions are placed in a locked cabinet.

Pregnancy test for women: All women of child-bearing potential will be asked if they are pregnant. If they are unsure, they will take a urine pregnancy test before the fMRI scan.

The subject may be asked to complete questionnaires or perform additional tasks specific to the scientific protocol. These will be reviewed and approved by the corresponding HSHBS-IRB.

Placement in scanner: All experiments will be carried on a 3Tesla MRI scanner (General Electric MR750, Waukesha, WI). When we position a subject in the scanner, head movement will be minimized through: (a) instructions to the participant; and (b) packing the head inside the head coil with a system of foam padding and pillows that we have found is well-tolerated by the participants, yet limits movement. Extra care will be taken to insure that the participant's head is

positioned as straight as possible since that eases the task of identifying landmarks used in positioning slices to be acquired in the fMRI scans.

Stimuli will be presented by a BrainLogics (PST, Inc., Pittsburgh, PA) digital MR projector, which provides high resolution video (1024 x 768) by back projection. An MR compatible lens system can correct for myopic or presbyopic subjects. He /She will be given ear protection. Responses will be recorded by an RF shielded button transducer, integrated with the E-Prime package (PST, Inc., Pittsburgh, PA), or equivalent software, for stimulus presentation control. Alternative stimulus presentation systems may be employed, but such changes are without consequences to the subject. In addition, eye movement monitoring via infra-red sensors built into the goggles may be used to record subject eye movements.

Physiological sensors, including a strain gauge to measure respiration, and plastic finger cuff, to measure heart rate by plethysmography, may be attached. These non-invasive sensors are FDA-approved components of the GE Signa Scanner, and are used in image reconstruction to remove physiological variance. They also permit online monitoring of the patient's physical state.

The MRI room is sealed off from the outside by a RF shield and the MRI technologist and team sit in an adjacent control room. Once in the scanner, subjects can communicate via intercom with the technician running the scanner in the control room. The MRI technologist can see the subject through a window that separates the control room from scanner room. In addition to the intercom system, subjects are given a squeeze bulb. They are informed that should they need to exit the scanner immediately or gain the attention of the technicians, they can trigger an alarm in the control room by squeezing the bulb.

The specific designs of the neuroscience experiments (audio-visual stimulation protocols, etc) will vary depending on the investigators and will undergo a separate review by the Behavioral Sciences IRB. The standard fMRI protocol is minimal risk as presented and applies only to IRB-HSBS research protocols with healthy adult subjects. The procedures described in this protocol are limited to the MRI scanning, as follows.

In addition to the routine scans, a research registry of the imaging data collected under this protocol will be created for future research purposes. Future research will require a separate IRB application to access registry data.

Risks

There is a risk that personnel not involved with the fMRI lab access fMRI research records. Only those directly involved in this study will have access to the research records. All records will be maintained in a locked cabinet in a room with limited access and/or in an electronic password protected file.

The standard fMRI protocol is minimal risk as presented and applies only to IRB-HSBS research protocols with healthy adult subjects. The risks associated with the fMRI study are:
A minor risk of discomfort or anxiety from being in the confined space of the MRI scanner.

1. Fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the subject.
2. Risks of hearing damage due to loud noises produced by the scanner.
3. Risk that the magnetic resonance image will reveal a minor or significant lesion in the brain, e. g. a tumor, previously unknown to the subject, and requiring additional follow-up.
4. Risk of injury from objects accelerated by the strong magnetic field of the magnet, striking the subject; or metallic substances on the skin or foreign bodies implanted deliberately or accidentally in the subject that acquire kinetic or thermal energy from the magnetic or radiofrequency emissions of the MRI, causing tissue injury to the subject.
5. Sometimes, subjects report a temporary, slight dizziness or light-headedness when they come out of the scanner.
6. Potential risk for pregnant women: According to the NIMH Council Workgroup on MRI research and Practices (September, 2005), "there is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risks under normal operating procedures." Nevertheless, subjects should be warned about potential risks, not yet discovered.

Minimization of Risks

The confidentiality of all information gathered directly from subjects is assured by assigning records a coded research number and identifying all computer and paper files only by this code. A single tracking file will link the codes with subject identifiers, such as their name. In addition, consent will be kept in a separate, locked room, apart from research data. All files will be kept in locked file drawers in locked rooms, to which only authorized research personnel have access. Only staff members who have a need to know personal identifying information will have access to this information.

Risks from MRI scanning:

1. The risk of discomfort and anxiety will be minimized by custom pads and pillows to make the subject as comfortable as possible. The subject is allowed to communicate with the machine operator via an intercom and may trigger an audible alarm at any time. Before the subject rolls into the bore of the magnetic, he or she is always reminded that they are free to stop the study at any time if they become uncomfortable. If they were to experience an anxiety reaction, the study would be halted, and the participant would receive immediate counseling from staff, with option to meet with the P.I. or another study psychiatrist. Participants find that once outside of the scanner, they experience immediate relief of any anxiety and discomfort. If the study team has any doubts about relief of anxiety, follow-up telephone calls would be made later that day or 1-3 days after the session to confirm the transient nature of their reaction.
2. The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low. The MRI pulse sequences will not use gradients that exceed 120 mT/m/s or RF pulses that exceed 1 Watt/Kg.
3. All subjects are required to wear foam earplugs to reduce the risk of hearing damage.
4. In the event of anomalous finding on MRI, the PI would contact the subject and explain that the subject should contact their primary care provider to obtain a clinical MRI scan (see Data Safety and Monitoring plan below for more details).
5. The MRI suite is kept clear of all objects that could be picked up by the magnetic field. MRI personnel are trained in safety procedures, which include training around the materials that cannot be brought into the scanner room. The technician administering the scan is also

trained to review each subject's MRI safety form to assess their suitability to enter the MR environment. Subjects are screened at multiple points. An initial phone screening is done, in which the MRI is explained and subjects are excluded from participation if they have contraindications to an MRI scan. On the day of the scan, the subject completes an MRI safety screening form, which is reviewed by study personnel and reviewed by the MRI technician. Subjects are prompted at two points to remove all metallic objects from their person, soon after the subject arrives at the MRI center. They are given instructions to empty their pockets, remove jewelry, watches, wallets, and shown a storage box where belongings can be safely stored. Immediately before entering the scanner room, they are prompted again, to ensure that they have removed any items that might interfere with the san or interact with the magnetic field.

6. To minimize risks from nausea, subjects are carefully eased out of the scanner, and a technician guides the subject as they arise from the scanner bed, counseling them to rise slowly, ensuring they have adequate balance.
7. Subjects are informed that pregnancy, or the intention to become pregnant, are contra-indications to receiving an research MRI scan. All women of child-bearing potential are asked about pregnancy or the possibility of pregnancy. When the subject is consented for the study, language in the informed consent document mentions this exclusion, again. All women of child bearing age will be given a urine pregnancy test the day of the fMRI scan. Woman with a positive pregnancy test will not be permitted to continue in the scanning study.

Incidental Findings

Incidental findings discovered in the course of a research scan have the potential to raise significant anxiety in subjects, while the nature of a research scan seriously limits the usefulness of the scan for resolving an incidental finding. At the first level, it is critical to make all participants aware of this risk. The University of Michigan IRB has considered this issue, and has issue standard consent language appropriate to warn subjects.

Another important consideration is to make subjects aware that they are receiving a research scan, which cannot be used to assess the clinical significance of any finding. The scans in this

protocol will not be read by a radiologist or other individual trained to evaluate the significance of a finding.

Standard operating procedure at the University of Michigan fMRI center does not entail reading of research MRI scans by neuroradiologists. Nevertheless, the experienced technicians and investigators collecting research data do encounter anomalous incidental findings, such as the presence of a large cyst or tumor. A protocol is in place to handle these events.

Discovery of a finding: Incidental findings that arise in the course of assessment, such as an abnormal finding in the MRI, will be brought to the immediate attention of the fMRI study PI.

Gathering additional information: The PI will review the finding, and seek consultation as appropriate.

Informing the subject: If the PI is available while the subject is being scanned, can assess the finding, and make a determination about informing the subject—it will be done immediately. If the PI is not available for a face-to-face meeting with the subject, study staff are instructed to complete as much of the protocol as is reasonable, without revealing the existence of an anomaly. The intention here is to control the circumstances by which the subject is informed of the anomaly, making sure that the PI is the person who talks to the subject, can answer questions and gauge the emotional reaction of the subject to the news. The subject will be informed by the PI, personally, either through a phone call or a face-to-face meeting. While a face-to-face meeting is preferred, this may not be immediately convenient for the subject, and the PI must weigh the relative benefits of the more personal setting versus anxiety engendered by anticipating a meeting to discuss something the subject did not expect to hear.

Informing the subject's health care provider: Arrangements will be made to provide a summary of the finding to the subject's personal physician, with the patient's permission. The information conveyed will recommend that a follow-up, clinical MRI be obtained to evaluate the incidental finding.

Informing the local IRB: The incidental finding will be reported to the IRB as an adverse event, with a gradation appropriate to the severity of the finding.

Inclusion and Exclusion Criteria

Any individuals older than 18 years of age can be included in this protocol except for those who are pregnant; those who experience claustrophobia or cannot lie still on their back for an hour; and those with ferromagnetic metallic or electronic implants in the body.

If the subject is unsure of whether she is pregnant, the FMRI laboratory will provide a urine pregnancy test at no cost to the subject.

In addition to these exclusion criteria, the lab will also follow specific study exclusion criteria in accordance with individual protocols, as specified by HSHBS-IRB.

Adverse Event Reporting

All adverse events related to the standard fMRI protocol or registry study will be reported in accordance with the IRBMED standard AE reporting guidelines.

Statistical Design

Each study will be responsible for their own statistical design as defined in their approved protocol.

The images collected will be subsequently analyzed using a variety of techniques, from morphometric analysis to linear regression, or independent component analysis, depending on the scientific question being asked by the researcher.