NON-INVASIVE MAGNETIC RESONANCE INVESTIGATIONS IN HEALTHY VOLUNTEERS

1. SCOPE

Many research groups within the Medical Sciences Division perform research measuring brain and nervous system structure and activity using Magnetic Resonance Imaging (MRI) scanners.

Magnetic Resonance Imaging (MRI) is safe and non-invasive and provides unsurpassed insight into the structure, organization and function of the living brain. The proposed MRI techniques, which use similar technology employed for clinical MRI examinations, are non-invasive and do not involve ionising radiation. While there are some risks associated with scanning some individuals (such as those with tattoos and some implants), these risks can be reduced when proper safety procedures are followed.

This approved procedure is intended for studies imaging the brain, central nervous system (CNS) and peripheral nervous system (PNS) using the University’s human MRI scanners. This approved procedure is intended for use when:

- The study involves only healthy volunteers, not recruited via the NHS.
- The study does not involve any pharmacological agents
- The study does not involve venepuncture or the collection of any biological samples.
- The study does not involve specific brain stimulation (e.g. TMS, TdCS)
- All answers in section B of the IDREC Checklist are “no” with the exception of B4

By measuring tiny magnetic signals from the blood or from nuclei (typically hydrogen) in different tissues, it is possible using MRI to characterize blood flow, tissue perfusion, metabolism and microstructure, as well as neuronal activity when the nervous system is at rest or performing a task. The specific types of MRI examinations that are performed vary in the nature of “pulse sequences”, or the precise timing and duration of radio frequencies applied for the examination and the ways in which they are observed. Typically, different types of pulse sequences may be applied in a single imaging session to gain different types of information.

The vast range of information that can be provided by MRI has led to an ever-expanding number of applications. However, these applications share the common feature that volunteers are asked to lie still on their back (in most cases) in the MRI scanner for periods of typically 45-90 minutes, and up to 120 minutes. Following safety screening, the participant is installed comfortably on the scanner table and given earplugs and/or MRI-compatible headphones to reduce scanner noise and/or to perform auditory tasks. Prism lenses or angled mirrors enable the volunteer to see outside of the scanner at all times and to view stimuli presented on a screen. During scans, the participant is monitored from the control room visually or via closed-circuit television. The volunteer in the scanner is able to contact the radiographer at all times using a call button and via an intercom system in the scanner. What varies between experiments, other than the pulse sequences, is the mapping of specific brain functions, biochemistry or physiology and the nature of the cognitive tasks that participants may be asked to perform. For this reason, we are submitting this general application for approval of MRI
studies of healthy adult participants. It would be supplemented by specific descriptions of individual sub-projects to be covered under this general approved procedure.

The 7 Tesla (7T) MRI scanner located at the Wellcome Centre for Integrative Neuroimaging (WIN – formerly FMRIB) operates at a higher magnetic field strength than typical clinical MRI systems. However there are many such systems installed world-wide and recent Health Protection Agency (HPA) and European (ICNIRP) advice has stated that field strengths up to 8 Tesla can be safely used as long as the participant is aware of the possibility of dizziness when moving into the MRI scanner.

The studies will involve characterisation of the basic structures, physiology and biochemistry of the CNS and PNS using MRI techniques. MRI sequences will include: task-related and resting functional MRI, task-related and quantitative ASL-based perfusion measures, structural measures based on T1, T2, proton density, susceptibility or diffusion-weighting, magnetic resonance spectroscopy, digitally-recorded, anonymised physiological monitoring and simultaneous electroencephalogram (EEG)/fMRI. At all times, participants will be able to indicate immediately if they wish to stop the scan by squeezing a call button or by requesting so verbally.

Functional MRI can be combined with other techniques offering higher temporal resolution, such as EEG, to take advantage of the different strengths of each technique. Simultaneous EEG-fMRI offers a particularly powerful tool when it is important to determine both the time-scale and the spatial location in the brain where a signal is processed. An approved procedure for stand-alone EEG imaging has been approved (CUREC_Approved_Procedure_IDREC_03). The only difference from stand-alone EEG measurements is that simultaneous acquisitions use specialized MRI-compatible EEG caps to take measurements during the MRI scan. MRI, EEG and combined fMRI-EEG imaging methods do not cause pain or harm to the participant. The proposed studies may or may not involve EEG acquisitions either in the scanner or outside of the scanner.

The targeted functions will include the way in which the CNS and PNS controls movement, experiences sensation involving audition, vision, somatosensation, generates or interprets language or solves problems. All participants will use combinations of the following types of stimuli: (i) sensory stimuli delivered through MRI compatible headphones (or similar), on a screen or by touch; (ii) texture or temperature change applied to the skin in a safe way; (iii) spoken or written language (words or passages) presented visually or aurally; (iv) tastes or smell delivered through MRI compatible systems; (v) pictures and drawings depicting emotional or non-emotional scenes. Responses will involve (i) simple motor movement including responses using a MRI compatible button box, pressure-pad or joystick; (ii) repetitive movements of parts of the body (e.g. fingers or foot) (iii) vocalizations, (iv) eye movement measured by MRI-compatible eye-tracking system, (v) vocalized responses recorded using audio equipment. Some participants may be asked to solve reasoning problems presented visually or verbally either with or without simple reinforcements (including small amounts of money). Importantly, these defined types of studies represent only standard fMRI designs with little associated hazard or discomfort for the participants. In studies where stimuli have explicit emotional valence, participant information sheets will give appropriate details.

Cognitive and performance measurements may be acquired outside of the scanner, during scanning or both, in testing sessions lasting about 30 minutes to two hours. The maximum time to be spent in a session in the scanner room will be two hours; if MRI scanning is accompanied by other tests, participants will be allowed to take at least 30 minutes’ break between test procedures. Therefore a
participant may be at the Centre for an entire morning/afternoon depending on the study. Questionnaires other than the MRI safety form, if used, will be detailed in study-specific applications.

2. TRAINING OF RESEARCH STAFF

All researchers at the Wellcome Centre for Integrative Neuroimaging (WIN – formerly FMRIB), the Oxford Centre for Clinical Magnetic Resonance Research (OCMR) and the Oxford Centre for Human Brain Activity (OHBA) undergo Good Clinical Practice (GCP) training in order to be involved in research involving volunteers. All researchers involved with MRI are required to undergo annual MRI safety training – failure to undergo this training will automatically involve revocation of access to the centres. All scanning will be conducted by a fully trained MRI operator or HCPC registered radiographer.

3. METHODS FOR RECRUITING PARTICIPANTS

Potential participants will be identified by poster adverts (sample enclosed) word-of-mouth and e-mail postings to departmental and college mailing lists, which will contain the contact details of the researcher who will send further study information sheets (sample enclosed) to interested participants. Contact details of study researchers will be detailed in individual study Adverts and Information Sheets.

4. INFORMATION PROVIDED TO PARTICIPANTS

The specific details provided to participants will vary depending on the study, but will always be on University headed paper, showing the department name and address. Specific statements relevant to MRI will include:

- the procedure for dealing with incidental findings
- MRI preparation procedures – removal of eyeliner, changing into scrubs, metal impregnated clothing etc.

The Information Sheet must be written in simple but non-patronising language. Most word-processing packages provide readability statistics for a document, and one should aim for a 12-year-old (Year 7) reading level for adults.

Please refer to, and use, the Information Sheet associated with this Approved Procedure

5. CONSENT OF PARTICIPANTS

Written consent will be obtained from all participants using the Consent Form associated with this Approved Procedure

Consent will be obtained for each study by a researcher trained in GCP, who will be named on the ethics application. Vulnerable populations or volunteers who are unable to provide informed consent will be excluded.

6. FINANCIAL AND OTHER REWARDS TO PARTICIPANTS

Compensation (either financial or in kind) may be offered to participants for their time and travel expenses. Some studies (for example, those investigating reward processing) may offer a
performance-related reward. Individual study proposals will detail the value (if any) of compensation to be offered. Compensation is limited to the time and inconvenience incurred as well as reasonable travel expenses and will in no circumstances consist of course credits for student volunteers.

7. POTENTIAL RISKS TO PARTICIPANTS/RESEARCHERS/OTHERS AND WHAT WILL BE DONE TO MINIMISE

MRI risks to participants

i) Comfort:
Certain 3T and 7T MRI sequences can be very noisy so participants will be given earplugs and or ear-defenders.

The enclosed space of the scanner can induce feelings of claustrophobia. All operators and radiographers are accustomed to dealing with participants who may be claustrophobic and have a variety of strategies to employ with people who exhibit feelings of claustrophobia but who still wish to participate in the study. Participants will be introduced carefully to the scanner and allowed to leave at any stage. Whilst in the scanner participants have easy access to a call button should they wish to stop the scan or speak with the radiographer or operator.

In order to reduce as far as possible the risks associated with MRI scanning, participants will be carefully screened for surgical or other implanted metallic devices as a result of surgery or accidents every time they attend for a scan. Furthermore, they will change into pocket less surgical scrubs for their scan.

Lying on the scanner table for prolonged times can induce temporary lower back pain. MRI-compatible pads and cushions may be used to improve participant comfort.

ii) Ferromagnetic Objects:
Ferromagnetic objects will not be permitted in the scanner room. Any stimulation or monitoring equipment with metallic components must be MRI safe or MRI compatible.

Any researchers entering the magnet environment will have undertaken annual MRI safety training and completed an annual Visitor MRI Safety Screening form to ensure maximal awareness and safety around the scanner. The research volunteers will complete a Volunteer MRI Safety Screening form for each and every visit unless they are attending twice on the same day.

Scanning with the 7T MRI Scanner

The UK Health Protection Agency has reviewed the safety effects of being exposed to a high magnetic field. It concludes that whilst participants exposed to magnetic fields of up to 8T experience various effects including dizziness, nausea, magnetophosphenes (which can be perceived as flashes of coloured light) and a metallic taste in the mouth, these effects were transitory and no long-term exposure effects were detected. These effects are related to field strength and the speed of movement through the magnetic field. The 7T MRI system limits the speed the participant moves into the scanner so these effects are minimised.
The information sheet and the operator will inform participants of the possibility of dizziness before they go in the scanner. If the participant does experience dizziness, the operator may choose to temporarily halt the table movement. The participant may choose to continue to the centre of the scanner where any adverse sensations dizziness etc. will gradually resolve, or they may choose to stop all procedures and come out of the scanner (either temporarily or to withdraw from the study).

**MRI risks to researchers**
As above, any metallic objects in or around the magnet will be designated MRI Compatible or MRI Safe to preclude projectile risks.

**Risks associated with EEG**
EEG recording has been used safely for many years (see CUREC_Approved_Procedure_IDREC_03) with no known cases of adverse events. EEG equipment to be used in conjunction with MRI scans will be in all cases certified as ‘MR conditional’ up to 3T field strengths. Hygienic use of the equipment will be ensured by soaking the EEG sensors, caps and the instruments used in applying EEG gel in disinfectant solution after each use. In the majority of cases, participants will wash their hair to remove gel at the end of each session (facilities are in place within the centres for this purpose) and MRI headrests are covered with clean paper towels for every participant.

8. **MONITORING AND REPORTING OF ADVERSE OR UNFORESEEN EVENTS**
The detailed images obtained from MRI scanners, while not suitable for clinical diagnosis, may on rare occasions identify unexpected structural abnormalities. If an abnormality is noted on the structural scan of a healthy volunteer, the WIN/OCMR/OHBA Standard Operating Procedure – Dealing with Neuro-Incidental Findings” will be strictly followed, unless the study documentation stipulates an alternative process.

In the event of an unexpected emergency incident, the emergency response team in the adjacent John Radcliffe Hospital covers WIN and OCMR. Emergency supplies (e.g. defibrillator) are available on site. For OHBA, researchers should telephone 999 as there is no emergency response team on the Warneford site.

9. **COMMUNICATION OF RESULTS**
Study results may be written up for publication in peer-reviewed scientific journals, presented at scientific conferences (in abstract or presentation formats), entered into fully-anonymised repositories of imaging data, submitted as part of course degrees and may form part of grant applications. In all cases, results will be fully anonymised and not contain any data that could be linked to the volunteers.

10. **DUTY OF CARE ISSUES / CONFIDENTIALITY**
Personal data (such as date of birth, and personal questions relating to MRI safety) as well as questionnaire responses may be necessary for individual studies. Study Information Sheets will detail this and explain that any personal information will be anonymised wherever possible, and information about volunteers maintained in strict confidentiality.

Occasionally, MRI studies identify abnormal anatomy or pathology in healthy volunteers. If an abnormality is detected, the WIN/OCMR/OHBA SOP – Dealing with Neuro-Incidental Findings will be
followed. The Principal Investigator would alert the Contact Radiographer who will make an initial assessment as to whether the abnormality may reflect a scanner artefact, or is of a trivial nature. Once an incidental finding is suspected, the Contact Radiographer will inform the Contact Clinician as soon as possible, who will meet with the Contact Radiologist at the John Radcliffe Hospital and together decide whether the finding warrants further clinical investigation. In this eventuality, the Contact Clinician would contact the volunteer directly and the appropriate action be discussed. The contact Neurologist maintains a database with anonymised summary information on the outcomes of all referrals.

Some studies may use validated questionnaires asking volunteers about state and trait anxiety and/or depression to interpret how these factors influence processing and perception of study stimuli. These questionnaires are not used for recruitment or screening purposes, however if a researcher, as a result of these questionnaires, has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress, CUREC guidance (BPG08) will be followed. The researcher will seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher if they are not clinically trained themselves.

11. DATA PROTECTION ISSUES

Imaging data is automatically coded at source with an anonymisation code that cannot be directly linked to the volunteer. Any electronic data (e.g. EEG files, behavioural reaction time files, questionnaires) will be labelled with a code number rather than a name or initials. Data is accessed via a password and firewall protected server. Anonymised data will be stored on archive tapes for up to 30 years. With the written informed consent of the volunteer, fully anonymised data may be shared with other research institutions, including researchers outside of the EU, for other and future research studies.

If it is necessary to retain any personal information (such as contact details), this personal information may be kept on a password-protected database, provided that the database is on an encrypted machine or on a protected server. The keys linking codes to personal details may be kept in lockable filing cabinets with access only by the University researchers, as stipulated on the ethics application. Personal data may be retained after the end of the study where the participant agrees to be contacted for future studies. For volunteers who do not wish to be contacted in the future, personally identifiable data will be shredded as soon as possible after completion of the study and within one year of completing study analyses. Personal data may be viewed by regulatory bodies and designated individuals within the University of Oxford for the purposes of monitoring and auditing the research with the written consent of the volunteer.

12. FURTHER INFORMATION

Sample consent form, participant information sheet and poster advert.
Title: Non-invasive Magnetic Resonance Investigations in Healthy Volunteers

13. CHANGE HISTORY

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<tr>
<td>3.0</td>
<td>Incorporates reference to the University Safeguarding Code of Practice and related requirements. Renamed ‘Approved Procedure’ (previously ‘Protocol’). Approved by CUREC, 19 November 2015</td>
<td>N/A</td>
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<tr>
<td>4.0</td>
<td>Removed requirement of study documents to be reviewed by CTRG prior to submission to the relevant IDREC</td>
<td>3.0</td>
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<tr>
<td>5.0</td>
<td>Changes made to reflect current processes at University scanning sites</td>
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<td>6.0</td>
<td>Change of site name from the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) to the Wellcome Centre for Integrative Neuroimaging (WIN) Removal of statement that previously excluded claustrophobic participants from taking part</td>
<td>5.0</td>
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