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Imaging Markers of Brain Network Dysfunction in Multiple Sclerosis

Healthy Volunteer's Information Sheet

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We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

In medical science, a 'marker' is something that can be measured (for example in the blood or urine, or on a scan) to monitor a biological process, disease or treatment response. In its 2013-17 Research Strategy, the multiple sclerosis (MS) Society calls for the development of better imaging markers that can be used in trials of new treatments for MS and MS symptoms. As new treatments are developed for treating problems with thought processes such as memory and concentration (referred to as cognitive processes) in MS, it is important to have a meaningful and easily-interpretable marker to show how organisation of brain networks alters in response to the new treatments.

We propose that a type of analysis called 'Graph Theory' (GT) will be able to provide meaningful and easily interpretable imaging markers of brain organisation from functional magnetic resonance images (MRI). GT is a type of mathematical technique for seeing how strongly different parts of a network are connected to each other. GT has been applied widely to study complex networks in science and society - for example, to characterise worldwide social networks on the internet, such as Facebook. Because different parts of the brain are linked together, they too can be thought of a forming a 'brain network' which we

can study with using MRI scans and GT analysis. The purpose of the study is therefore to investigate whether or not markers derived from GT analysis of brain networks relate to cognitive processes, and how stable those markers are over time.

Why have I been invited?

You are being invited to take part because you are healthy. You were recruited based on your age and gender. We are inviting 60 participants like you to take part: 30 people with MS and 30 healthy volunteers without MS.

Because the study includes an MRI scan, you are eligible to take part only if:

- There is no possibility that you are pregnant
- You are not severely claustrophobic
- You do not have any implants or devices (e.g. aneurism clips, pacemakers, defibrilators, stents, cochlear implants, metallic internal fixations)

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

Participation requires one attendance lasting no more than 3 hours. A researcher will contact you to arrange a time that is convenient. Three days before the session, a researcher will contact you by telephone to confirm the time, and to check that you are well-enough to take part.

The MRI scanner at QMC that will be used for the study

A researcher will meet you at the entrance to the Queen's Medical Centre. You will go to a private room where the researcher will explain the study to you and answer any questions you have. If you have decided you would like to take part, you will be asked to sign a consent form. The researcher will go through a set of questionnaires with you to test various cognitive processes. You will then go to the MRI scanner inside the Queen's Medical Centre, where a researcher will check that it is safe for you to be scanned. You will then have an MRI scan of your brain, lasting

approximately 40 minutes. Inside the scanner, you will simply have to lie down and relax without falling asleep.

Expenses and payments

Healthy volunteers will be reimbursed £10 per visit for travel, parking and inconvenience caused as a result of taking part in the study.

What are the possible disadvantages and risks of taking part?

Provided you do not have a condition which prevents you from having an MRI scan, there are no risks associated with this study. You will be screened for conditions preventing you from having an MRI scan before you have the scan.

Magnetic resonance imaging uses radio waves similar to those used in radio and TV transmission. These have a much lower energy than X-rays and are therefore considered safe to humans. We will be following strict national safety guidelines which are designed to prevent the theoretical hazards of MRI which are burns and electric shocks. Such accidents have very rarely occurred elsewhere. While there is no evidence to suggest that MRI is harmful during pregnancy, it is advised not to scan pregnant women. We have decided not to test for pregnancy as routine but if you think you may be pregnant you should not be scanned.

The MRI scanner is a relatively enclosed space and occasionally participants can feel claustrophobic. During the scan you are able to speak to the researchers performing the scan. If you would like to come out of the scanner at any time, you can request this. If you know that you are claustrophobic, we would advise against you participating.

In the unlikely event that a potential abnormality is identified on the scan by one of the researchers, the images will be reviewed by a qualified consultant radiologist working within the Radiological Sciences Research Group. If the suspicion of a significant abnormality is confirmed, the findings will be explained to you by the radiologist and details of the findings sent to your General Practitioner. The radiologist involved will advise on appropriate measures which will need to be taken in light of the findings, which may include performing further scans or referral to an appropriate hospital-based specialist, both of which would be arranged by your General Practitioner. The finding of a significant unexpected abnormality may have benefits in that it may be possible to offer treatments earlier than would otherwise have been possible. However, participants should also be aware that the finding of significant abnormality may adversely affect employment and insurance status.

What are the possible benefits of taking part?

We cannot promise the study will help you personally, but if it provides a marker that can be successfully employed in trials targeting cognitive symptoms in MS, it is possible that in future, improvements will be made to the management of such symptoms, including fatigue.

In terms of producing knowledge, we anticipate the resulting publication of two scientific papers, with one of potentially high-impact. The work completed in the study as part of an educational programme will increase the capacity for future MS research, by helping to train capable researchers, and by developing and improving partnerships between the involved parties (such as those between research institutions, the health sector and local MS communities). The study results could also inform future product development.

What happens when the research study stops?

Upon completing the research study, you will not be contacted further (unless you wish to hear the results of the study). Data will be analysed and kept on a secure server for 7 years after the end of the study. Scientific manuscripts will be prepared and submitted to journals for dissemination.

What if there is a problem?

In case you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator. If this route fails to achieve a satisfactory resolution and you still wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you. The Patient Advice and Liaison Service (PALS) can be contacted for further assistance at the QMC by calling 0800 1830204.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Any information about you which leaves the research unit will have your name and address removed so that you cannot be recognised from it. Your personal details will not be passed onto any third parties.

All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number, email) will be kept for 1 year after the end of the study so that we are able to contact you about the findings of the (if you inform us that you do not object to being contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data. Should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis. No further data would be collected or any other research procedures carried out on or in relation to you.

What will happen to the results of the research study?

The MRI scans and questionnaire scores will be used by researchers in the Radiological Sciences Research Group or collaborating researchers to understand how brain network organisation relates to cognitive performance and fatigue in MS patients. The results will be written-up as part of a PhD thesis and published in peer-reviewed scientific journals. The results of the study are likely to be published between 2014 and 2016 in journals such as *Neurology*, *Brain* and *Human Brain Mapping*. In addition, the MS Society regularly disseminates news about the results of the research they fund. You will not be personally identified in any publication.

Who is organising and funding the research?

This research is being organised by the Radiological Sciences Research Group in the University of Nottingham and is being funded by the UK Multiple Sclerosis Society.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the "East Midlands – Nottingham 2" NHS Research Ethics Committee. We performed a pilot study in 10 participants with MS, who all agreed that the scanning and assessment were acceptable. The chief investigator attended a charity-run MS support centre and was able to discuss the research idea with the centre manager and present individuals with MS.

Further information and contact details

If you would like to discuss the study further or would like more information, please feel free to contact the chief investigator:

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General information and useful links regarding participation in clinical research is provided by the People in Research website: http://www.peopleinresearch.org

If you require assistance or have a complaint, you can contact the University of Nottingham School of Medicine at +44 (0) 115 8230018 or by email at medicine@nottingham.ac.uk.