



PAIN RELIEF FOUNDATION

PATIENT INFORMATION SHEET

Title of Study: Mapping of Cortical Reorganisation and Targeted Brain Stimulation for Chronic pain, a TMS Study

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You are being invited to take part in a research project. Before you agree to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends or relatives, and your GP if you wish. Take your time to decide whether or not you wish to take part.

Thank you for taking the time to read this leaflet.

What is the purpose of this study?

We know that the way the brain takes in what is happening in the body changes if a person develops chronic pain. Doctors have been able to show which parts of the brain are not working quite as they used to work before the pain. If the brain can be changed back to how it used to work, maybe pain will be better. In this study we wish to see if we can successfully do this using a new treatment. This is called transcranial magnetic stimulation, or TMS.

What is transcranial magnetic stimulation (TMS)?

TMS is a painless way to "switch on" very small parts of the brain by a magnetic pulse. Magnetic pulses surround us everywhere, thanks to the earth's magnetic field. When you had your brain scan, magnetic pulses were sent through your head. When magnetic pulses are used for treatment, they need to be delivered in a particular way. Firstly, we need a tool that is designed for the purpose. The tool we use in TMS is a coil that sends the magnetic pulse through the skull into the brain. The coil, made of plastic coated copper wire, looks like a paddle or a large spoon and is held in place by the investigator. Secondly, we need an individual's brain scan to be used as a map for the investigator so that he can direct the pulses to a very precise location in the brain. When the pulse reaches the superficial layer of the brain, it generates a tiny electrical current. The brain then finds a way of using this current to improve its activity. (For those who are more technically minded we have added a detailed description of how the TMS machine works, found at the end of this leaflet).

Why have I been chosen?

You suffer from chronic pain which has not responded sufficiently to the treatment you have received. Your doctor has decided that your pain is related, at least in part, to alterations in the way your brain responds to sensations from your body. You have previously had an MRI of the brain.

Do I have to take part?

It is up to you whether or not you agree to take part. If you do decide to take part you will be asked to sign a consent form. If you do decide to take part and then change your mind you are free to do so at any time without giving a reason. This will not affect your normal medical care.

What will happen to me if I agree to take part?

If you agree we will ask you to fill in questionnaires (with help if needed) about your pain and to keep a pain diary for one week. You will then come to the Pain Research Institute Sensory-Motor Laboratory in the Clinical Sciences Centre where the research takes place. The building is next door to the Walton Centre (directions will be provided). You will be asked first to attend one or two sessions, during which we will use TMS to make a map of your brain so that we can target treatment. Following this we will ask you to attend 5-10 separate sessions for treatment. You will be offered reimbursement for travelling expenses which you might incur during test visits.

We may also ask you to attend one or two extra sessions so that we can take some measures of activity in your brain.

Before the first treatment session, and after the last one, we will ask you to undergo a simple set of tests to measure how your skin responds to different temperatures and pressures, called quantitative sensory testing (QST).

How is TMS given and what will I feel?

You will be seated comfortably and your head will be resting on a padded support. We will measure your head and send this information to the TMS computer. This will only take a few minutes. You will wear a special set of goggles which will measure the movements of your head. This information is used to provide a map of your head position to the computer which has a copy your previous brain MRI. The technique is similar to that used in Sat Nav devices. In this way we can target the TMS pulses from the coil to within 2mm accuracy.

There will be a clicking noise associated with the current passing in the coil, but the effects are not painful. However, you may notice some twitching of the scalp muscles or nearby nerves.

If we need to stimulate the part of the brain related to movements of your hand for example, we will place recording electrodes on your hand (or your foot, depending on where your pain is). These electrodes are small (1 cm in diameter) plastic discs stuck on to the skin and are painless. The information is used to measure the best target for the TMS pulses.

During the first 1-2 sessions, while we are making an accurate map of your brain we will use TMS pulses strong enough to cause a small movement (twitch) in your arm, leg, neck or head (depending on where your pain is), lasting a fraction of a second. Other parts of the brain, when stimulated, may not lead to any movement or sensation. Mapping usually involves 20-25 pulses given every 5-15 seconds. During the actual TMS treatment (5 – 10 sessions), a lower intensity is chosen so that you may feel nothing, or a vague sensation in the area of your pain. Sometimes we may intentionally stimulate a part of the brain which may not be

related to your painful condition. The treatment is given in sets of pulses lasting 10 seconds every 30 seconds, up to 20 sets. One treatment session will last approximately 30 minutes, including the preparation time.

Do I need to prepare for this treatment in any way?

No preparations are needed. At your first visit we will assess your suitability for TMS. There are a few reasons why some people should not have TMS. You must be over 16, not be pregnant, not have a cardiac pacemaker, not wear a cochlear implant, and not have a brain or high spinal cord stimulator in place. If you have ever suffered from fainting fits, we can only perform TMS if the information from your doctor is that they have not been epileptic fits. If you have a history of drug or alcohol abuse, or if you have severe heart disease, we must check with your doctor that you are eligible. Some types of medications may effect the brain responses and we will assess each person carefully to make sure the TMS is safe

Is TMS safe? What are the side effects?

TMS is generally considered safe but there are some safety issues you should know about. There are international guidelines that have been in force since 1998, updated in 2009, which we will follow carefully. The TMS coil causes a clicking noise which can sound quite loud if it is near the ear so you will be asked to wear earplugs. Some subjects feel a little dizzy or may have a slight headache afterwards but these very rarely require any treatment. TMS pulses activate small muscles and nerve endings in the scalp which may be a little uncomfortable, but less than 1 in 50 people feel it is too uncomfortable to continue.

Some patients have experienced an epileptic seizure after TMS. Since guidelines have been in force, they have become very rare. A recent review reported 2 cases of epileptic fits in tens of thousands of sessions of TMS. We believe the risk of a single seizure exists but is very small. The risk can be minimised by carefully assessing each person. We do not offer TMS to people who have had a fit in the past or are using high doses of medication known to make fits more likely. The investigators are trained in how to deal with a fit in the very unlikely event of one happening. The investigators who either give or record your responses to TMS are medical doctors. It should be underlined that TMS does not cause actual epilepsy. There are no reports of patients continuing to have epileptic seizures after their TMS treatment has been terminated.

If you have an epileptic seizure triggered by TMS, you will need to notify the DVLA by law. You will also have to stop driving. There is no strict advice available about what happens next, and DVLA will deal with each case on an individual basis. After having heard from their Medical Advisor, you may be asked to return your driving licence to DVLA. If you have a group 1 licence and you are asked to surrender it, you can get it back after 6 months, provided that you have been assessed by an appropriate specialist, and investigations such as an EEG or brain scan are normal. The rules are much stricter for those with a group 2 licence. You must remain seizure-free for 5 years, and have normal brain studies before you can start driving again. Before taking part, you should discuss the matter with the study doctors and your specialist doctor or your GP.

What happens during quantitative sensory testing (QST)

We will ask you to undergo QST twice, before and after treatment, if you suffer from neuropathic pain (e.g., nerve injury pain, spinal cord injury pain, central post-stroke pain, trigeminal neuropathy). This diagnosis will have been confirmed

at the time of assessment of your eligibility for the study. QST involves several different components. First, we will measure the sensitivity of the skin overlying your main pain area by gently prodding the skin with a series of nylon fibres to measure the lightest touch you can feel. Next we will warm and cool the skin with a small metal plate to measure how you detect changes in skin temperature. We will then test whether your skin is sensitive to touch, by brushing the painful area and then gently prodding with a stiff nylon filament for a few seconds. Finally, we will repeatedly brush the skin to see if this causes more pain, and do the same with the nylon filaments. We will first test a normal area of skin on the opposite side of your body, and then the painful side. Although these tests are very gentle, because of your skin sensitivity, they may cause you some temporary discomfort.

What are the possible disadvantages of taking part?

Apart from possible mild discomfort caused by TMS and the need for several sessions for treatment we are not aware of any disadvantages. Please note the comment about the safety of TMS above.

What are the possible benefits of taking part?

The treatment may be helpful. In centres in which a similar method is used, reports suggest that approximately 40% of people with chronic pain are helped. Because TMS is a new treatment we cannot guarantee that the results in our laboratory and in our patients are the same as elsewhere. Also, we do not yet know how long any positive effect may last.

What if new relevant information becomes available?

Should any new information regarding the effects of TMS become available, your research doctors would carefully consider its impact. This could mean either changing the way TMS is given, or possibly withdrawing you from the study.

What will happen if I do not wish to continue to take part in the study?

You are free to withdraw from the study at any point. We would use whatever data we have collected from you for the planned analyses, unless you specifically tell us not to.

If I benefit from the treatment can I have it on the NHS?

There is no TMS service available anywhere in the NHS for the management of chronic pain. However, we will be very interested in continuing to provide the treatment for you in the form of monthly "boosters" for up to one year. In the meantime we plan to start another research study where the effects of long-term TMS are assessed. If such an extension study starts, you may wish to consider taking part.

Where can I get more information about this treatment?

The International TMS Society has a website that you can access. There are several websites maintained by hospitals and research centres (e.g., Mayo Clinic at <http://www.mayoclinic.org/medicalprofs/transcranial-magnetic->

[stimulation.html](#) and Brookehaven Medical Department at <http://www.bnl.gov/medical/tms/default.asp>).

Are there alternative treatments?

There may be, and your doctor will be able to detail them. In case of chronic pain, alternative treatments include medication and neurosurgical procedures. Some patients may be considered for a particular type of neurosurgery if they respond well to TMS but the effect is not long-lasting enough.

Will my taking part in this study be confidential?

All information collected during the course of this research will be confidential. Any information gathered from you will be numbered so will not have your name or details on it. You will be asked to give consent to allow regulatory authorities to scrutinise the information we have collected from you during the study. Unless you disagree, we will inform your GP of your participation in this study and its purpose.

What will happen to the results of the study?

Results from all participants will be compiled for scientific reports that will be submitted to medical journals for peer review and publication. The data collected during the research will be held by the investigators in a secure place.

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal Walton Centre complaints mechanism will be available to you.

What do I have to do now?

If you wish to take part, we ask you to contact us at 0151-529-5750 (Prof. Nurmikko's secretary). We will then send you the pain diary and a number of questionnaires to fill in before your first session. We will give you the directions to the Sensory-Motor Laboratory.

Contact for further information:

Dr. Paul Sacco and Professor Nurmikko will be able to answer any questions either via e-mail (P.Sacco@liverpool.ac.uk ; tjn@liverpool.ac.uk) or by phone (0151 529 5820, 0151 529 5835).

Additional Information on Navigated Brain Stimulation (NBS)



NBS is a procedure which allows us to study the activity of the brain using a brain MRI scan and a non-invasive technique called transcranial magnetic stimulation (TMS). In TMS, a current passes through a coil of copper wire that is encased in plastic and held over the subject's head. This coil resembles a paddle or a large spoon and is held in place by the investigator. As the current passes through the coil it generates a magnetic field that can penetrate the subject's scalp and skull and in turn induce a current in the subject's brain. There is a clicking noise associated with the current passing in the coil, but the effect of the magnetic field and the induction of current in the brain are not painful. However, some discomfort may occur from the contraction of scalp muscles or the activation of nearby nerves.

TMS was introduced in the mid 1980's and is used in clinical neurophysiology to study the nerve fibres that carry the information about movements from the brain cortex to the spinal cord and the muscles. This technique is felt to be safe and is part of standard clinical testing in neurology in many countries worldwide.

Technical developments in the devices used for TMS made it possible in the late 1980's to apply TMS in trains of multiple stimuli per second. This form of TMS is called repetitive TMS or rTMS. In rTMS, stimuli are applied to the same brain area several times per second during several consecutive seconds. The number of stimuli per second, the strength of the stimuli, the duration of the train of stimulation, the interval between trains, the total number of trains and the total number of stimuli in a given session or to a given brain position can all be varied. All these aspects of rTMS are referred to as stimulation parameters.

The development of integrated systems allowing the registration of anatomical structures and coil positions with MRI landmarks allows the application of TMS to be targeted to specific cortical areas (within 2mm accuracy).

Repetitive TMS can be used to study how the brain organizes different functions such as language, memory, vision, or attention. In addition, rTMS seems capable of changing the activity in a brain area even beyond the duration of the rTMS application itself. In other words, it seems possible to make a given brain area work more or less for a period of minutes, hours, days or even weeks when rTMS is applied repeatedly several days in a row. This has opened up the possibility of using rTMS for therapy of some illnesses in neurology and psychiatry.

Repetitive TMS can be applied in a single session or in different sessions on different days. A single or multiple brain areas might be targeted by rTMS depending on the reason for the study. Generally investigators are interested in studying if and how rTMS changes a given brain function or the symptoms of a given disease.