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Pioneers in nerve stimulation and monitoring

THE GUIDE TO MAGNETIC STIMULATION

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The New Guide to Magnetic Stimulation

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The ability of a transient magnetic field to induce an electrical current within body tissue permits the researcher and clinician to influence or monitor functions of the neuromuscular system and to affect sensory neurons in the brain. It is able to reach deep neural structures such as the motor cortex and spinal nerve roots, non-invasively and without pain.

The effects of magnetic fields have been a source of research and interest, and indeed of fear, since Faraday's experiments showing magnetic flux coupling in the early part of the nineteenth century. Magnetic fields are able to pass unhindered through skin, muscle and bone and would therefore potentially be useful in the examination of human tissue if the magnetic field were to have any effect on the tissue through which it passed.

Fortunately, a time-varying magnetic field will induce an electrical current in any tissue through which it passes, and therefore magnetic fields can be used to stimulate muscles, peripheral nerves and cortical neurons without surgical access or anaesthetic agents.

This guide provides an overview of the techniques involved in magnetic stimulation, from first principles through to some of the clinical applications now feasible. Also included are details about different stimulator types and the effects of different waveforms, and a look at more recent developments. A list of reference papers organised by discipline is available separately as a supplement to this guide. We thank our readers who have contributed helpful information or suggestions towards this edition.

Please note that this guide describes the state of the art in magnetic stimulation and is intended for a world-wide readership. Some techniques and magnetic stimulator devices described represent uses that are considered as investigational in the USA. In particular this applies to the use of cortical magnetic stimulation. Further details on the regulations governing the use of investigational devices can be obtained from the FDA (www.fda.gov).

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Part 1: Fundamental and Technical Aspects

Brief History

Electromagnetic induction was first described by Michael Faraday in 1831 at the Royal Institution of Great Britain. It is probably the most relevant experimental observation for magnetic stimulation. Faraday wound two coils on an iron ring and showed that whenever the coil on one side was connected or disconnected from a battery, an electrical current passed through the coil on the other side. The iron ring helped to position the coils in relation to each other and an experiment a few weeks later produced the same effect from two coils closely positioned in air. With non-invasive magnetic stimulation the stimulating coil acts as the first coil, air as the medium for the flow of the magnetic field, and the electrically conductive living body tissue as the second coil.

In 1896 d'Arsonval [C R Soc Biol; 1896, 3: 450-51] reported phosphenes (flickering lights in the visual field) when placing his head between two coils driven from an alternating 110 volt supply at 30 amperes. It is now known that this was due to the direct stimulation of the retina. Silvanus Thompson repeated and confirmed this experiment, as shown in Figure 1.

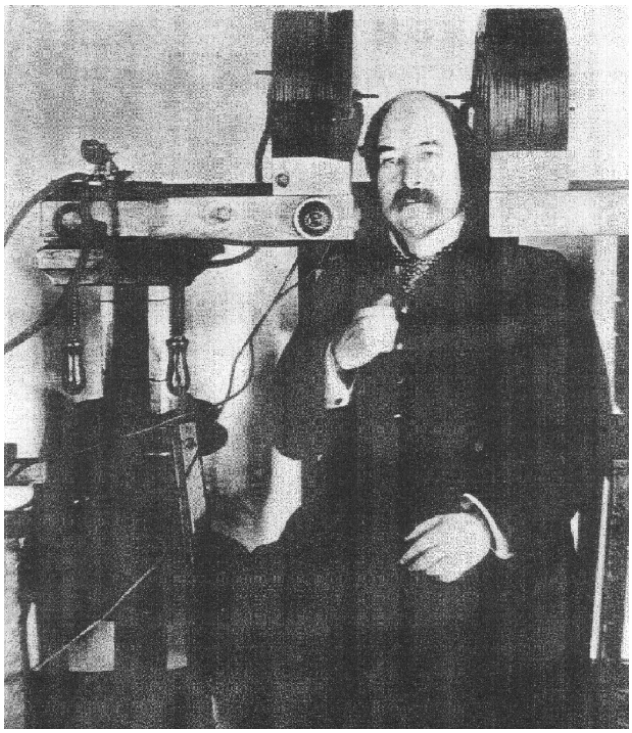


Figure 1: Silvanus P. Thompson with his experimental equipment; the two coils can be clearly seen

Bickford and Fremming in 1965 [Digest 6th Int Conf Med Elec Biol Eng, 1965, p112] demonstrated the non-invasive magnetic stimulation of facial nerves. In 1982 Polson et al. produced a magnetic stimulator capable of peripheral stimulation and recorded the first muscle evoked potential [Med Biol Eng Comput, 20: 243-4]. The technique of magnetic stimulation came of age in 1985 when Barker et al. in Sheffield [Lancet, 1985, 1106-1107] achieved magnetic stimulation of the human motor cortex. For a more detailed historical review the reader is referred to a publication by Geddes LA [J Clin Neurophysiol, 1991, 8:1-9].

Progress has been rapid since 1985 with several new areas of research using new developments. Equipment reliability has been improved, and stimulators with differing output waveforms developed. Coil design has been as important as stimulator development, the most important advance being the development of coils with multiple windings for precise stimulation of nerves or cortical neurons. Other developments have included trains of pulses for therapy in rehabilitation, sports medicine and in the treatment of psychiatric disorders; the use of fast repetitive stimuli to determine the laterality of speech centres; and high energy focal stimuli as an adjunct to ECT to relieve drug resistant depression.

Principles of Magnetic Stimulation

The first commercial magnetic stimulators were produced in Sheffield in 1985 and the Magstim Model 200, based on the original Sheffield design, was launched in 1986. Stimulator information given in this document is based on the current Magstim 200^2, which has replaced the original machine using the latest technology.

The Magstim range of magnetic nerve stimulators are developed under an exclusive licence with the University of Sheffield. Magnetic nerve stimulators typically consist of two distinct parts: a high current pulse generator producing discharge currents of 5,000 amps or more; and a stimulating coil producing magnetic pulses with field strengths up to 4 tesla, and with a pulse duration from 100μs to 1ms, dependent on stimulator type. A block

diagram of a typical stimulator is shown in Figure 2; a transformer charges a capacitor under the

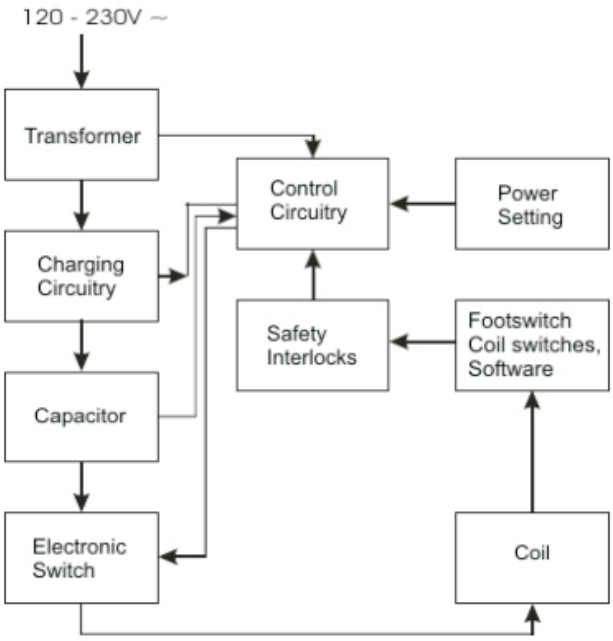


Figure 2: Block diagram of the Magstim 200[2] monophasic stimulator

control of a microprocessor, which accepts information such as the capacitor voltage, power set by the user, and various safety interlocks within the equipment to ensure proper operation, and the capacitor is then connected to the coil via an electronic switch when the user wishes to apply the stimulus.

The discharge current of c.5,000 Amps flows through the coil and lasts for up to 1ms, but 90% of the discharge occurs within the first 100µs. This is important because it is the rate of change of the magnetic field which causes the electrical current within tissue to be generated, and therefore a fast discharge time is crucial to stimulator efficiency (see figure 12). The discharge current flowing through the stimulating coil generates the necessary magnetic lines of force as shown in Figure 3. As the lines of force cut through tissue, a current is generated in that tissue, whether skin, bone, muscle or neural; if the induced current is of sufficient amplitude and duration such that the cell membrane is depolarised, neuromuscular tissue will be stimulated in the same manner as conventional electrical stimulation.

It is therefore important to understand that a magnetic field is simply the means by which an electrical current is generated within the tissue, and that it is the electrical current, and not the magnetic field, which causes the depolarisation of the cell membrane and thus the stimulation of the target muscle/nerve.

Since the magnetic field strength falls off with the square of the distance from the stimulating coil, the stimulus strength is at its highest close to the coil surface. The stimulation characteristics of the magnetic pulse, such as depth of penetration, strength and accuracy, depend on the rise time, peak electrical energy transferred to the coil and the spatial distribution of the field. The rise time and peak coil energy are governed by the

	Circular 50mm P/N 9999	Circular 70mm P/N 9762	Circular 90mm P/N 3192/3	Double 25mm P/N 1165	Double 50mm Prototype	Double 70mm P/N 3190/1	Double Cone P/N 9902	Cooled Coil P/N 1640	Placebo Coil
Inside diameter (mm)	25	40	66	18 (x2)	34 (x2)	56 (x2)	96 (x2)	56 (x2)	N/A
Outside diameter (mm)	77	94	123	42 (x2)	74 (x2)	87 (x2)	125 (x2)	87 (x2)	3190 casing
Number of turns	18	15	14	14 (x2)	11 (x2)	9 (x2)	7 (x2)	9 (x2)	N/A
Inductance (µH)	13.5	16	23.5	10	23	15.5	17.8	16.4	2.55
Peak Magnetic Field Strength (Tesla)	3.6	2.6	2.0	4.0	N/A	2.2	1.4	0.93	0.2
Peak Electric Field Strength (V/m)	600	530	530	660	N/A	660	N/A	N/A	N/A
Number of discharges @ 100%	65	63	145	40	78	60	584	>>3600	984

Table 1: the physical characteristics and maximum calculated outputs of the coils used with the Magstim 200[2]

electrical characteristics of the magnetic stimulator and stimulating coil, whereas the spatial distribution of the induced electric field depends on the coil geometry and the anatomy of the region of induced current flow.

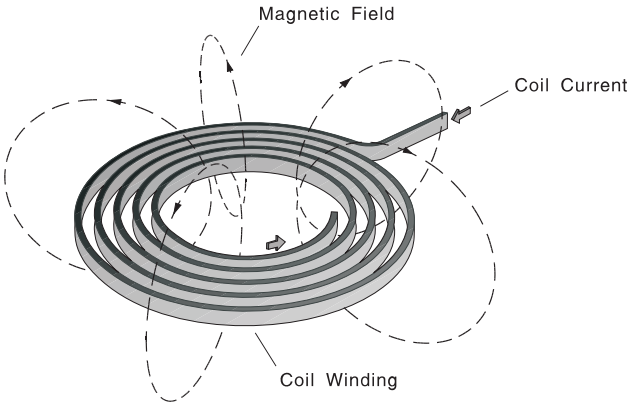


Figure 3: a circular coil showing the lines of force generated when current flows through the winding

Stimulating Coils

The stimulating coil consists of one or more tightly wound and well-insulated copper windings, together with temperature sensors and safety switches. The physical description of some of the coils used with the Magstim 200^2, with their estimated magnetic and electrical fields, are shown in Table 1.

Single Coils

A circular 90mm mean diameter coil is supplied as standard with single pulse systems. This coil is most effective in stimulating the human motor cortex and spinal nerve roots. A more recent development is the remote control coil which allows the user to operate the stimulator from control buttons situated on the coil handle. To date, circular coils with a mean diameter of 80-100mm have remained the most widely used in magnetic stimulation. A 3D representation of the magnetic field produced on the surface of a 90mm circular coil is shown in Figure (Type 9784 in Table 1). In the case of circular coils it is important to note that the induced tissue current is near zero on the central axis of the coil and increases to a maximum in a ring under the mean diameter of the coil. Stimulation occurs under the winding and not under the coil centre.

During the stimulating phase, when the magnetic field is increasing from zero to its maximum, the induced tissue current flows in the opposite direction to the coil current. In the case of the Magstim 200^2, all single circular coils are marked with Side A and Side B. With the coil placed on the body and Side A visible, the induced tissue current flows in the clockwise direction, indicated by an arrow pointing in a clockwise direction on the coil surface. With Side B visible, induced tissue current flows in the anti-clockwise direction, again indicated by an arrow. The use of the correct coil side is particularly important in cortical stimulation as the human motor cortex is more sensitive when the induced current is flowing from posterior to anterior. With the coil placed centrally on the vertex and Side A visible, the induced current predominantly stimulates the left motor cortex and hence the right side of the body; with Side B visible the right motor cortex is stimulated and the response will occur on the left side of the body.

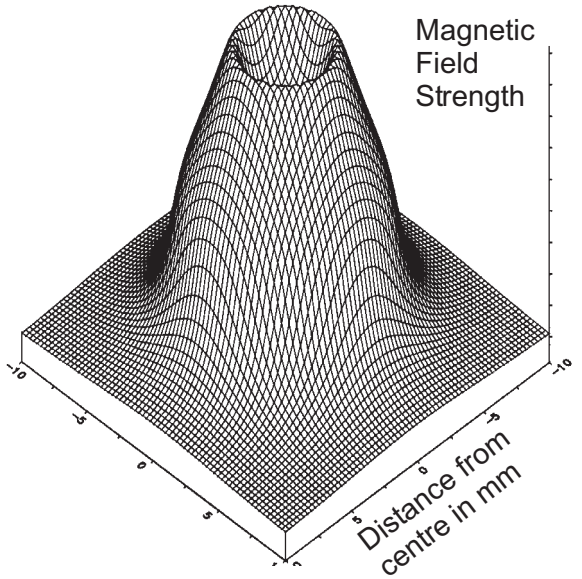


Figure 4: the magnetic field plot of a 90mm circular coil

Double Coils (Butterfly/Figure of Eight)

The most notable improvement in coil design has been that of the double coil (also termed butterfly or figure of eight coil). Double coils utilise two windings, normally placed side by side. A 3D representation of the magnetic field produced on the surface of a 70mm double coil (Type 9925 in Table 1) is shown in Figure 5. Typically double coils range from very small flat coils for brain mapping work to large contoured versions designed to stimulate deeper neural structures in the brain. The main advantage of double coils over circular coils is that the induced tissue current is at its maximum directly under its centre, where the two windings meet, giving a more accurately defined area of stimulation. A remote control

double 70mm coil is supplied as standard with the new Magstim 200[2].

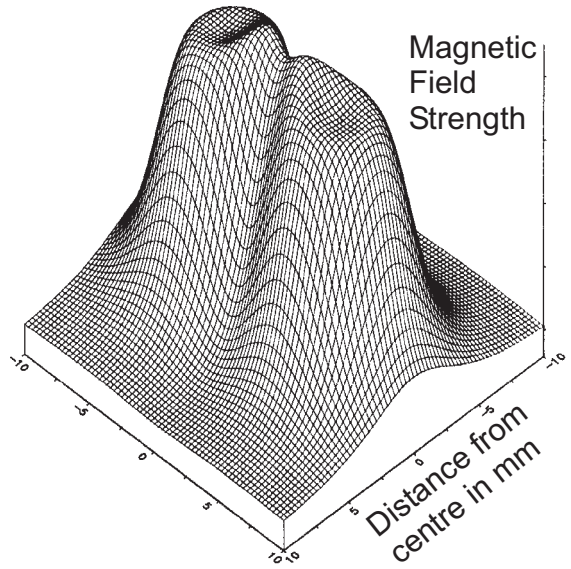


Figure 5: the magnetic field plot of the double 70mm coil

areas controlling the muscles of the lower torso and limbs.

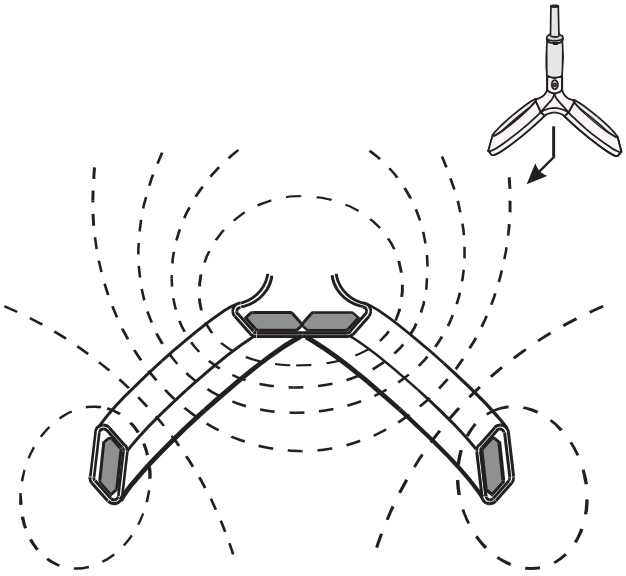


Figure 7: diagram showing the concentration of the lines of force appertaining to the double cone coil

Special Coils

The Double Cone Coil (Type 9902)

Figure 6: the double cone coil, designed to fit overhead near the vertex and stimulate the lower limbs

The Double Cone Coil (Figure 6) has two large cup shaped windings positioned side by side, with a flat central section and angled sides closely fitting the patient's head. The coil geometry allows for better magnetic coupling, giving significantly higher induced current in the central fissure (70% higher than with the 90mm circular coil). Figure 7 illustrates the effect of angling the coil windings, showing that the lines of force are concentrated in the area underneath the central area of the coil. This coil is useful in stimulating the motor cortex

Double 70mm Air-Cooled Coil (Type 1600-00)

This coil uses a forced air flow to cool the coil surface so that it can be used for long trains of pulses. It is usually used in conjunction with the

Figure 8: the air cooled coil; air is sucked across the surface of the coil, with the heated air removed through the tubing

Magstim Rapid stimulators, enabling long protocols to be completed, or to allow several subjects to be treated in a morning or afternoon session.

Small Double Coils

15-25mm for research applications. (1-2T output)

Figure 9: a double 25mm coil used for phrenic nerve stimulation or in animal studies

These small diameter coils are built to enable precise stimulation of superficial structures, since the depth of penetration of the magnetic field is related to the diameter of the coil windings. These coils are also used in animal research, often to stimulate rats.

Because they are of small diameter, and use lighter gauge copper for the windings, they will be able to stimulate fewer times before overheating when compared to the larger diameter coils.

Sham (Placebo) Coils

These coils are designed to be used by researchers who wish to complete blind or double blind trials. Sham coils consist of 2 coils, one active, one passive, but which look and feel identical. It is only possible to determine which is the active coil by checking the serial number of the coil.

The active coil is a standard coil which is connected via a box to the stimulator; the sham coil looks identical, and is also routed via a box. Inside the box, in the case of the sham coil, most of the energy is discharged; a small portion of the current is taken to the coil head and discharged into a small coil so that the characteristic ‘click’ is heard when the stimulator is fired. In addition, this small coil, which is built into the housing of the standard coil, is sufficient to stimulate the skin and muscle overlaying the scalp, thereby giving the patient the sensation of magnetic stimulation, but without the penetrating stimulus of the larger coils.

MRI coil

A coil suitable for use in a MRI scanner has been developed. The stimulator is located outside the MRI room, with the coil cable, via an extension, being fed through the wall so as to maintain the Faraday cage; the coil itself is designed to minimise the artifacts generated by placing a metallic object within the scanner. At present, the coil is suitable for use in 3T scanners; more powerful scanners may lead to the coil being damaged which could damage the scanner.

Custom Coils

Figure 10: a small selection of special coils built for individual customers

The Magstim Company is unique in manufacturing special coils for individual customers. These coils are built either to a customer’s own specification, or as a variant of a standard coil to enable particular research to be undertaken. Custom coils usually have a polyurethane coating rather than plastic covers, but the safety of the coils is maintained through advanced insulation techniques. The only limits are your imagination and practical safety!

Stimulating Coil Construction

The stimulating coil is the only part of a magnetic nerve stimulator which needs to come close to, or into contact with, the patient. During the discharge of the magnetic pulse the coil winding is subjected to high voltages and currents. Although the pulse generally lasts for less than 1ms, the forces acting on the coil winding are substantial and depend on the coil size, peak energy and construction. Careful coil design is, therefore, a very important aspect in the safe construction of a magnetic stimulator. Large coils utilise more copper mass than small coils and generally have a lower

electrical resistance. As a result, less heat is dissipated in their windings and because of their higher heat capacity they remain usable for much longer periods of time without becoming warm.

Magnetic Field Strength vs. Stimulus Strength

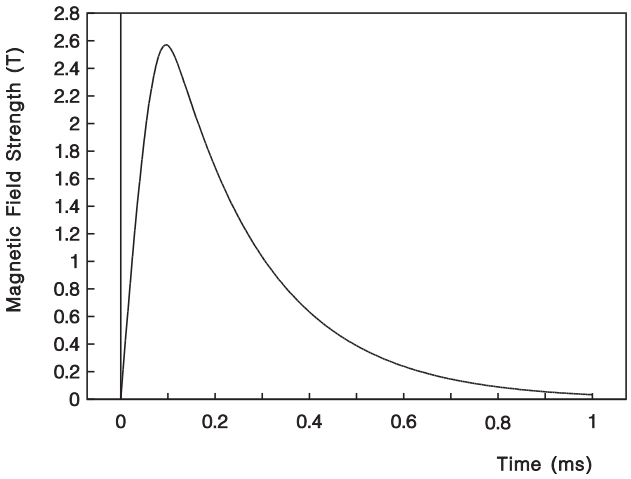


Figure 11: the magnetic field plot against time for the 90mm coil, measured at the coil surface

Magnetic field strength (as shown in Figure 11) alone is a poor measure of magnetic stimulator performance. The suitability of a coil for its intended application must be taken into account. Magnetic field strength is defined as the magnetic flux density and does not reflect the total magnetic flux produced by the stimulating coil over its total area. In a small coil where the magnetic flux is concentrated in a small area, the magnetic field intensity will be higher than in a larger coil, but the field reduces much more rapidly with distance. Hence a small coil is somewhat more powerful in the stimulation of superficial nerves and a large coil is more suitable for structures at depth.

The electric field, as shown in Figure 12, is a better measure of the efficiency of the coil, as it shows that the greater part of the stimulus occurs within the first 100μs, whereas the magnetic field rises to a maximum at 100μs and then slowly decays for up to 1ms. However, it is the *rate of change of the magnetic field*, rather than simply the magnitude of the field, which has the more important role to play in the efficiency of the coil design. This is more clearly demonstrated by the electric field plot.

The amplitude, waveform and spatial characteristics of the induced current all play a role in magnetic nerve stimulation. As examples, the 90mm coil is very effective in bilateral stimulation of the phrenic nerve roots, the double 70mm is used for mono-hemispheric transcranial

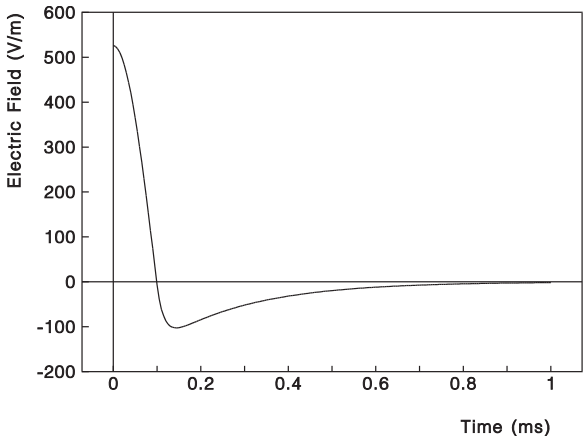


Figure 12: the electric field plot against time for the 90mm coil, measured at the coil surface

stimulation, the circular 50mm coil is well suited to stimulation at Erbs point, and the double cone is most powerful in cortical stimulation of the lower extremities.

Part 2: Types of Magnetic Stimulators and their Related Area of Function

The Magstim 200, 220 and Rapid systems have now been replaced by the Magstim 200², 220² and Rapid 200².

Magnetic Single-Pulse Systems

Single Pulse Systems may be used for cortical or peripheral stimulation with either single circular or double figure of eight coils. A single pulse is of

Figure 13: The Magstim 200² single pulse magnetic stimulator and remote control double 70mm coil

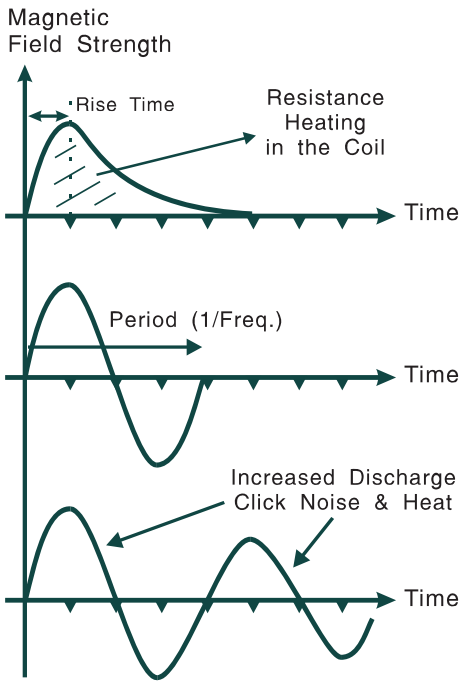
value in producing a temporary lesion used to investigate visual detection, discrimination, attention and plasticity. It is also an aid in the brain mapping of motor sites and in evoking motor responses to aid in neurological diagnosis.

Figure 13 shows the Magstim 200² and a double 70mm stimulating coil. This machine, and its predecessor, the Magstim 200, are widely used in neurology departments throughout the world to evoke motor responses from patients undergoing a clinical neurological examination. Its ability to stimulate without pain makes it useful to both patient and clinician, and its property of being able to stimulate the motor cortex makes it a unique form of stimulation.

Types of output waveform

A single pulse may be monophasic, biphasic or polyphasic. Each of these has its own properties and so may be useful in particular circumstances. For neurology, single pulse, monophasic systems are generally employed; for rapid rate stimulators, biphasic systems are used as energy must be recovered from each pulse in order to help fund the next; and polyphasic stimulators have yet to be developed as clinical machines, but may have a role in therapeutic applications. The different output waveforms are summarised in Figure 14.

Monophasic: The Magstim 200² produces a monophasic pulse with no current reversal. Monophasic discharge currents reduce heat



Monophasic

For: More accurate than biphasic, lower noise, lower heat

Against: Not easy to obtain bilateral cortical responses

Biphasic

For: Short efficient pulse, suited to bilateral cortical stimulation

Against: Higher noise, possibly less accurate than monophasic

Polyphasic

For: Efficient, suited to bilateral cortical stimulation

Against: Highest noise and heat; less accurate than monophasic

Figure 14: the output waveforms of monophasic, biphasic and polyphasic stimulators

dissipation in the coil, discharge click noise, stimulus artifact and increase stimulus accuracy in comparison to biphasic stimulators. In addition, the stable and well defined monophasic pulse allows for a better understanding of the mechanisms involved in magnetic nerve stimulation, particularly when used for cortical stimulation.

Biphasic: The Magstim 220[2] provides a biphasic

Figure 15: The BiStim system, showing the master unit (top), the slave unit (bottom), and the BiStim module (top left)

pulse, which is short and efficient and well suited to bilateral cortical stimulation. Its balanced charge and short duration pulse make it the most suitable choice for use with a double coil for studying brain connectivity in the MRI. However, it produces a higher noise level and is possibly less accurate for cortical stimulation when used with a circular coil. The output power of a biphasic stimulator is about 20% less than the comparative output of a monophasic stimulator.

Polyphasic: Efficient and well suited to bilateral cortical stimulation when used for MEPs, but less accurate than monophasic, and produces the highest heat and noise of the three pulse types.

Magnetic Pulse Pair Systems

Paired-pulse systems deliver two magnetic pulses through one coil and have the ability to stimulate cortical inhibitory and excitatory interneurones and also corticospinal output neurones.

Paired pulse systems are built using two separate Magstim 200[2] units and a BiStim module, which connects them together and controls the pulse delivery, as shown in Figure 15. If the customer already owns a Magstim 200[2], then it can be easily expanded to produce the second pulse.

The new Magstim 200[2] units are not compatible with the old Magstim 200 units, and so cannot be

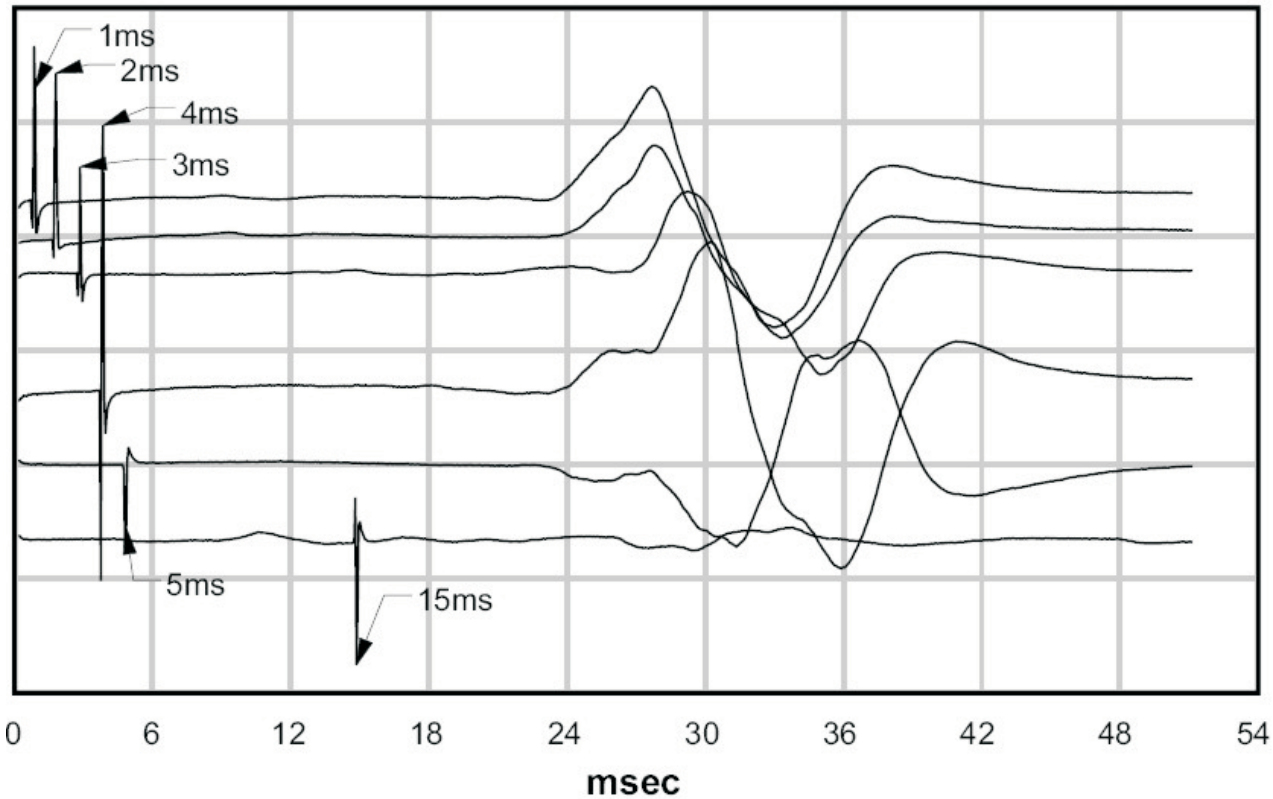


Figure 16: the effect of varying the interpulse spacing - cortical stimulation of ADM

'mixed and matched' to create a BiStim system. This is because the new BiStim system has one major capability which the old system did not; the ability to combine the two pulses and simultaneously discharge the two stimulators into a single coil. This produces a pulse c.120% of maximum output, and can be very useful when trying to establish a supra-maximal threshold in particular subjects.

BiStim Set-up

The BiStim set-up provides the flexibility to evoke either an inhibited or a facilitated response through two pulses with a pre-selected interpulse interval, and individually adjustable power levels, to give either a sub- or supra-threshold stimulus. It can deliver two single pulses through one or two coils, or deliver a combined pulse for extra power through one coil. The BiStim set-up utilises two Magstim 200^2 units and a BiStim Module, as illustrated in Figure 15. Using the BiStim Module it is possible to adjust both the power level and the timing of each pulse independently of each other, within the range of 1ms to 1 second, or to have an effective timing of 0ms - a combined pulse. It is not possible to have an interpulse spacing between 0ms and 1ms.

The BiStim system may be controlled either by the User Interface mounted on the Master Unit, or by use of the remote coil facility, allowing the individual power settings of each stimulator to be chosen as well as the interpulse spacing. Figure 15 shows a BiStim system with both a User Interface and a Remote Control coil, but only one of these options is actually necessary for correct operation. The lower to the two Magstim units does not even require the User Interface, shown on the right of the picture, as its functions are usurped by the Master Unit (on top) or the remote control coil. However, using 2 units with their own User Interface controllers does mean that the 2 units can be separated and used in different departments, which cannot be done if there is no User Interface.

Delivering two spaced pulses through one coil maintains the same induced current flow resulting from each pulse. In the case of cortical stimulation the site of stimulation may not remain the same, as the first pulse, depending on whether it is a sub or supra threshold stimulus, can activate inhibitory or facilitatory mechanisms and modify the threshold and readiness of other sites to stimulation by the second pulse. For this reason, most studies using magnetic pulse pairs have used double (figure of 8) coils for selective stimulation. The BiStim Module is allowing the detailed study of the inhibitory and facilitatory mechanisms of the brain and spinal cord.

Two superimposed pulses may be delivered through one coil to give extra power to help overcome an abnormally high subject threshold or for use where the normal peripheral stimulus has been insufficient for a supra maximal muscle response.

The effect of varying the interpulse spacing during cortical stimulation is demonstrated in figure 18. Whilst short interpulse spacings have the effect of facilitating a muscle response, a longer delay will inhibit a response. An interpulse spacing of about 4ms gives the greatest facilitatory response, but by 15ms the response has become inhibited. This therefore allows the researcher not only to measure a subject's 'normal' thresholds, but also to devise experiments which can make use of these physiological properties.

Silent Period

The silent period is a physiological phenomenon whereby a second, much delayed EMG response is seen after stimulation when the muscle is facilitated. Figure 17 shows the cortical stimulation of ADM and the second response, and gives a value of 140ms for the silent period for the author, with slight facilitation of the muscle.

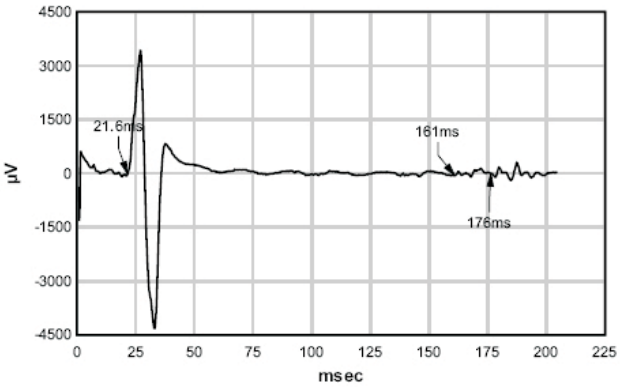


Figure 17: cortical evoked potential to ADM showing silent period; 161ms - 21.6ms ≅ 140ms

Repetitive Magnetic Stimulation

Repetitive magnetic stimulators are produced in two basic types: fixed frequency, where each pulse in a train has the same interstimulus interval,

typically ranging from 20ms - 1000ms intervals, and the power output is the same for each stimulus; and modulated frequency, where the intervals between each pulse in a train can be

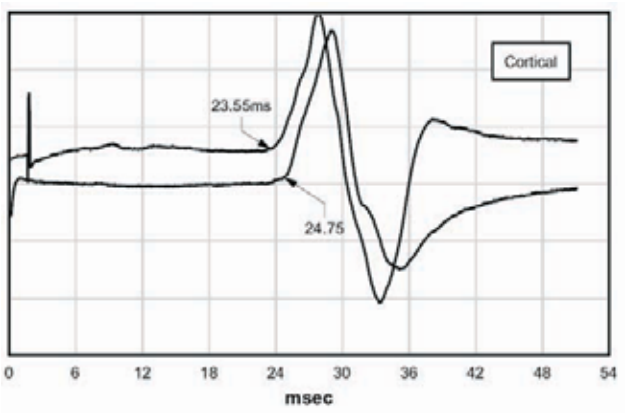


Figure 18: an example showing the effects of facilitation using a BiStim; the lower waveform shows cortical stimulation of ADM using a single pulse; the upper waveform shows stimulation of ADM using the same coil and power setting, but with a conditioning pulse 2ms before the second pulse - the spike at the start of the screen shows the stimulus artifact. The latency to the first peak is shown to demonstrate the effect of facilitation caused by the conditioning pulse. Note the greater amplitude of the facilitated response, and the shorter latency. The muscle was relaxed in both cases.

varied from 1ms - 1000ms and are selectable in 1/10ms steps, and the power of each stimulus may vary. The Magstim Rapid and Super Rapid are fixed frequency machines whereas the BiStim has a modulated frequency. Fixed frequency machines can supply trains of pulses lastings several seconds; modulated frequency machines offer only a discrete number of pulses, usually 2, but limited only by budget. Generally speaking, fixed frequency is useful in therapeutic applications and modulated frequency provides a more sophisticated approach to cortical investigation.

Cortically applied rTMS in psychiatric and psychological research has indicated potential benefits when used in the investigation and treatment of a variety of mood disorders. The technique also opens a window into the brain for the study of connectivity and cognitive and behavioural neurosciences. The use of rapid-rate stimulation has been extended to studies of depression, schizophrenia, mania, epilepsy, Parkinsons disease, pain relief, and the induction of speech arrest, to determine the laterality of the speech centre.

Peripherally, applied repetitive magnetic stimulation can aid with pain relief. It may also assist spinally injured patients who are unable to micturate when they feel the need or to remove

Figure 19: the Standard Rapid package with optional trolley, showing touch sensitive screen, MEP Pod and double 70mm coil

the feeling of urgency when it is not. These techniques may be of particular interest to the urologist or to patient carers. Repetitive stimulators are also providing a role for peripheral stimulation in the relief of spasticity for both stroke and multiple sclerosis, and in muscle stimulation to simulate a cough in spinally injured patients.

Figure 20: the Super Rapid showing trolley, coil stand, double 70mm coil and MEP Pod

Because of the lack of pain associated with magnetic stimulation, it is able to stimulate induced electrical currents into both superficial and deep muscle layers and to stimulate deep nerves such as the sciatic and femoral. This enables the clinician to look at muscle strength, fatigue and

recovery, and aid in the maintenance of muscle bulk during a period of incapacity, using power levels above those that would cause peripheral damage or tissue necrosis if electrical stimulation were used. This gives rTMS an exciting potential in the world of Rehabilitation.

Cortically applied rTMS can induce a seizure under certain circumstances, but the risk can be minimised through the use of carefully selected parameters. Before using cortical rTMS the clinician is recommended to study a milestone paper covering safety issues [Wassermann EM, Electroencephalogr Clin Neurophysiol, 1998, 108: 1-16]. As well as a comprehensive set of guidelines the paper contains one table which sets a train duration limit based on stimulating power and frequency. This is an excellent starting point for a study.

Repetitive stimulation equipment is now available from all major magnetic stimulation manufacturers, some of whom have safety features built into their control programs. These programs allow accurate dosage to be determined, with the three main parameters being power level, frequency and train duration (or pulse number).

Development of the new Magstim Standard Rapid 200^2 and Super Rapid 200^2 have resulted in improvements in operational use and safety, and permit protocols to be installed or written to specification and precisely delivered. These protocols will automatically be up-dated with safety parameters built into the control program. The information about subject, date, time, frequency, power levels, train duration etc. is automatically logged onto a removable non-volatile media for later recall and analysis, or can be printed to hard copy if required.

The setup screen of the Session Software protocol controller is shown in Figure 21. This illustrates the degree of control which can be obtained over the trains of pulses delivered; the Start Time, Power, Frequency Duration and Wait Time can be different for each train. The program contains interlocks to prevent illegal entries, as well as safety interlocks to prevent stimulation protocols which could induce a seizure. This can be over-ridden by the user, but only after further interlocks have been brought to the user's attention, and a definite decision made to alter the safety protocols.

The new machine also offers higher rates of stimulation, up to a maximum of 100Hz. Maximum output power is maintained up to 30Hz for the Magstim Super Rapid 200^2, and falls to 50% output power at 50Hz. At 100Hz, the output power is reduced to 20%. This means that the machine is unlikely to be effective if the brain is stimulated at these higher frequencies, but there are likely to be applications in peripheral stimulation for rehabilitation.

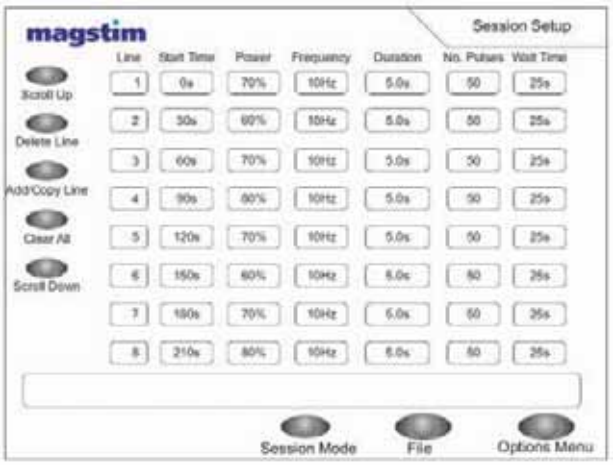


Figure 21: the Session software screen showing the parameters which can be controlled by the program

Brainsight™ Frameless

Frameless Stereotactic Image Guided TMS System

Brainsight™ Frameless is a stereotactic image guidance system specifically designed for use in transcranial magnetic stimulation and was developed to address the issues of coil placement accuracy and of coil location monitoring.

The system provides a means to improve the accuracy and the repeatability of positioning a TMS coil over a particular target on a subject. As well as provide tool(s) to maintain and monitor the position of the tool to ensure that a constant stimulation location is maintained throughout the procedure.

Frameless stereotaxy was first developed for neurosurgery, having evolved from an older method of matching medical images to the patient using a stereotactic frame as the common coordinate system. This frame is fixed to the patient's head before imaging, and is designed to act as a tool holder to allow the surgeon to guide tools to the desired location in the brain.

Frameless stereotaxy uses a position sensor instead of a stereotactic frame to define the "real world" coordinate system. A registration, or matching procedure, is performed to calculate the mathematical relationship between the position sensor coordinate frame and the coordinate frame of the images.

Once this relationship is established, tools tracked by the position sensor (i.e. TMS coil) may be introduced and their position and orientation may be mapped to the image coordinate frame. This allows the frameless stereotaxy software to display a representation of the tools over the images.

Brainsight™ Frameless is a stereotactic image guidance system that facilitates the positioning of TMS coils over a subject's brain. It displays coil and stimulation targets derived from MRI / fMRI images on anatomical images, providing an interactive, navigational guide for coil positioning, a technique called Image-Guided TMS.

Image-Guided TMS involves positioning of a magnetic stimulator coil over a specific location of the scalp to deliver a magnetic field into a precise location within the brain. This magnetic field is applied to induce a selected set of neurons to fire. Frameless stereotaxy can be helpful here because it is advantageous to position the tool based on targets within the brain (or as seen on images of the brain).

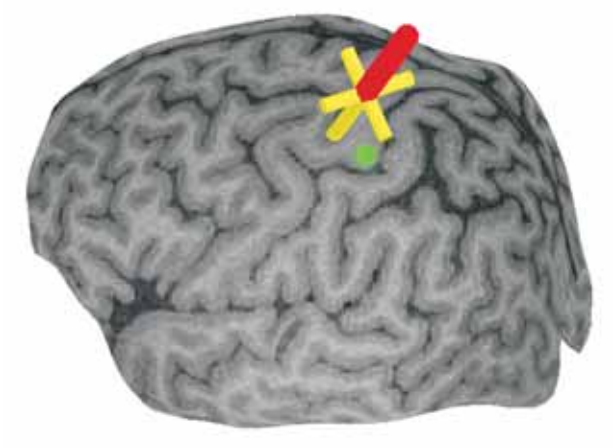


Figure 22: Curvilinear reconstructions can effortlessly be performed in minutes and provide an intuitive and informative display of coil location and brain anatomy in 3D visualisation and real-time

Figure 22 shows a manually selected stimulation target illustrated by the green dot and a representation of the stimulating coil.

Patient MR images are co-registered using anatomical structures that are easily identified on both the MR images and the patient. Landmarks are identified on the MR images by selecting and dropping anatomical landmark points and subsequently identified on the patient using a Pointer Tool. Typically, Brainsight Frameless utilises four easily identifiable anatomical landmarks, these being the bridge and tip of the nose, and the tragus of each ear, as shown in Figure 25.

Figure 23 shows co-registered MRI/fMRI subject data. fMRI data can be overlaid on MR images to provide functional target areas identified by activity data captured within the fMRI.

In Figure 24, both anatomical position and trajectory of the stimulating coil can be recorded using a trajectory marker which records not only the coil's position over the cortex, but also records the coil's trajectory in two planes. This is important when targeting structures below the surface of the brain.

References

Fernandez E, Alfaro A, Tormos JM, Climent R, Martinez M, Vilanova H, Walsh V, Pascual-Leone A. *Mapping of the human visual cortex using image-guided*

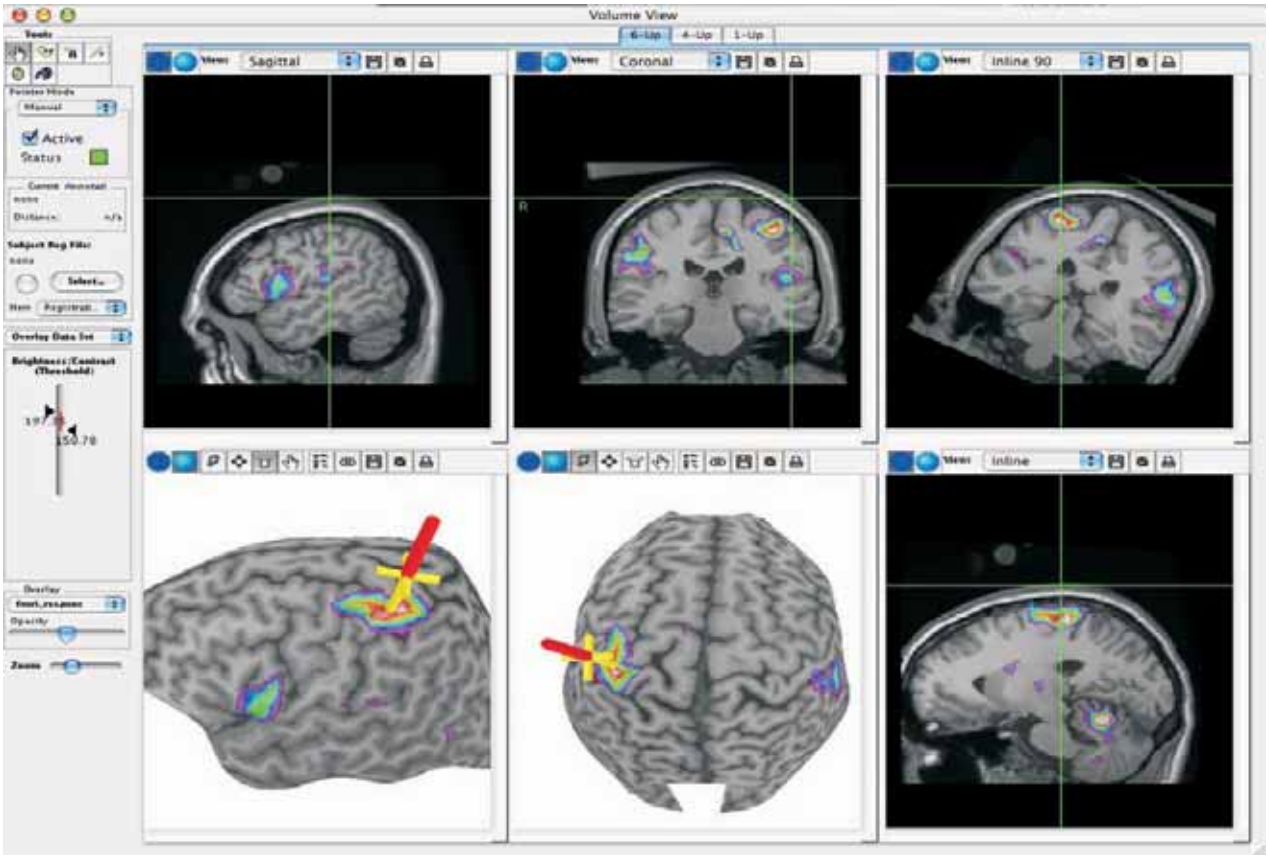


Figure 23: Targets can be defined based on anatomical and functional information

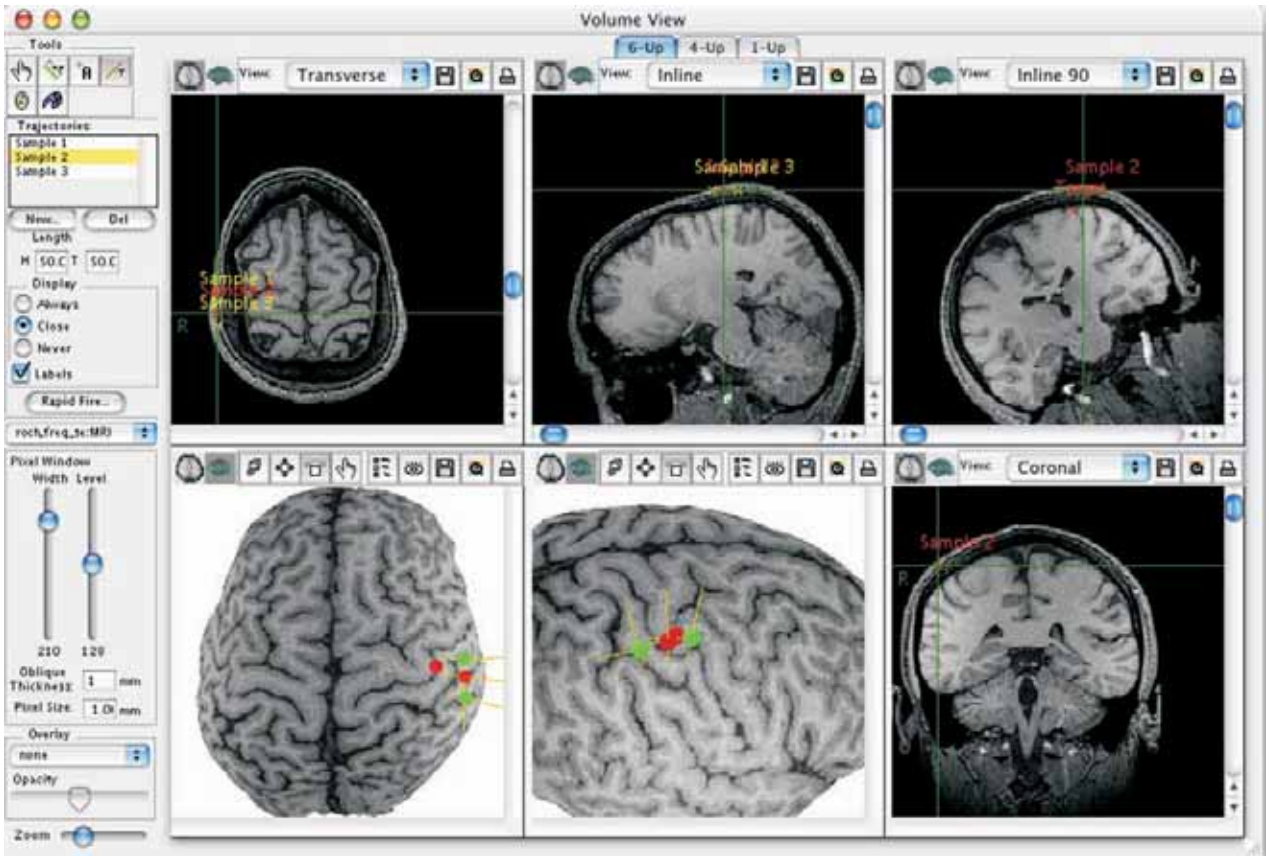


Figure 24: Enables coil location and trajectory to be recorded for archiving and correlation with stimulus results.

transcranial magnetic stimulation. Brain Research Protocols 10 (2002) 115-124.

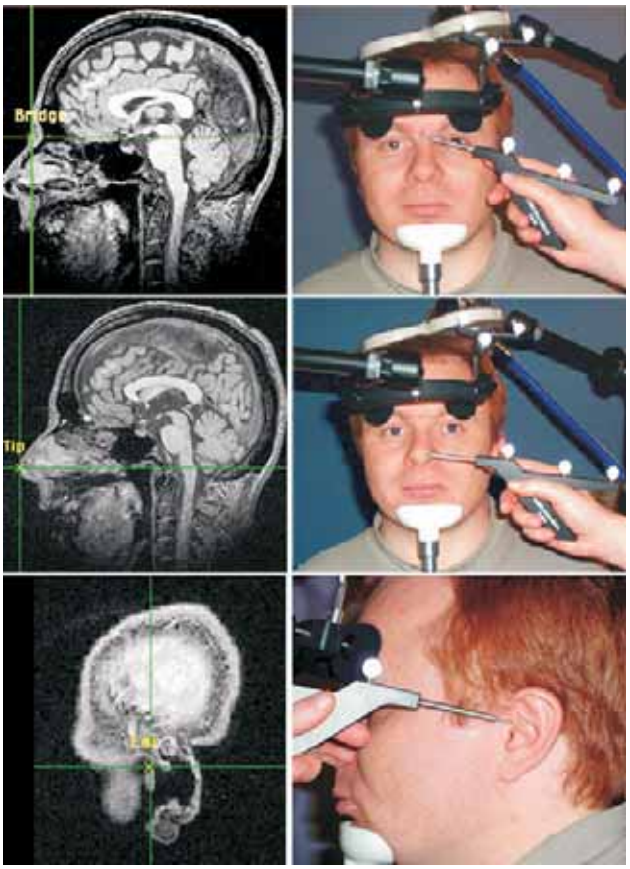


Figure 25: Co-registering a subject with anatomical structures allows Brainsight™ Frameless to implement 3D coil targeting

Rushworth MFS, Hadland KA, Paus T, Sipila PK. *Role of the human medial frontal cortex in task switching: A combined fMRI and TMS study.* J Neurophysiology, 2002; 87:2577-2592.

Rushworth MFS, Ellison A, Walsh V. *Complementary localisation and lateralisation of orienting and motor attention.* Nature Neuroscience volume 4, #6, June 2001

Paus T. *Imaging the brain before, during, and after transcranial magnetic stimulation.* Neuropsychologia. Feb 1999; 37(2):219-224.

Paus T, Wolforth M. *Transcranial magnetic stimulation during PET: reaching and verifying the target site.* Hum Brain Mapp. 1998; 6(5-6):399-402.

Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. *Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex.* J Neurosci. May 1 1997; 17(9):3178-3184.

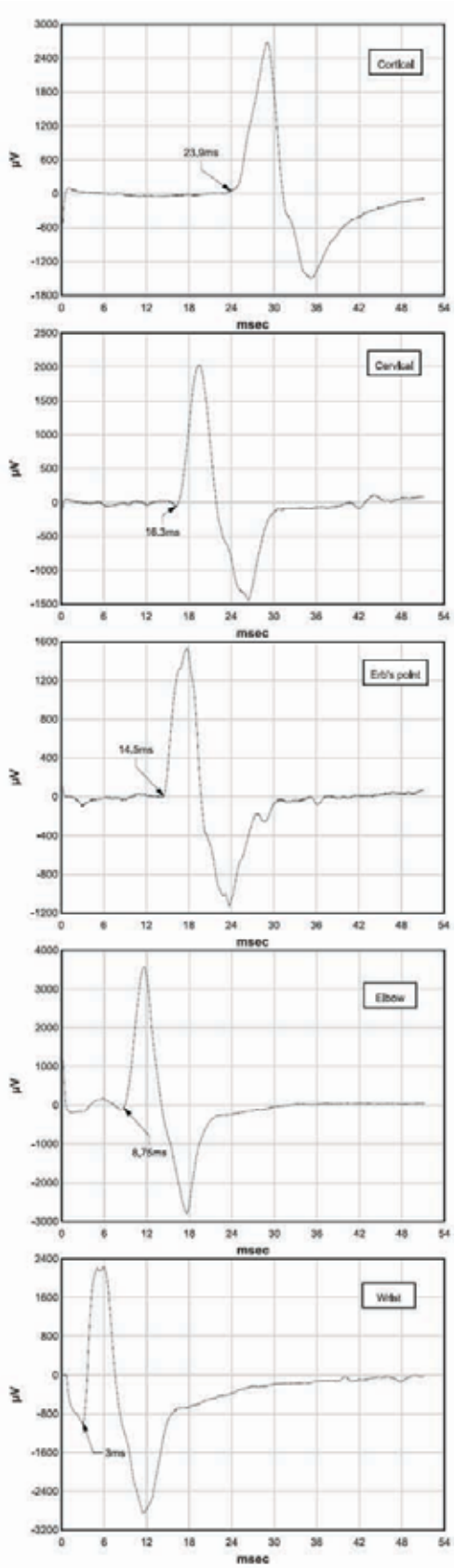


Figure 26: responses from ADM when stimulated at motor cortex; C7 cervical root; Erb's point; the elbow; and the wrist, using a double 70mm coil

Comeau R, Peters TM, Paus T. *Optically based frameless stereotaxy for image guided transcranial magnetic stimulation (TMS).* Presented at Human Brain Mapping annual meeting, Dsseldorf, 1999: Poster presentation.

Part 3: Clinical Aspects

Magnetic stimulation can safely and easily stimulate most neural structures, unimpeded by fat and bone, and without discomfort. The majority of the clinical applications are for the non-invasive stimulation of the peripheral and central motor pathways. Other uses include stimulation of the left and right prefrontal cortex, visual cortex, language centre, cerebellum and peripheral sensory nerves. These applications cover uses for diagnosis, prognosis, monitoring and therapy. The following sections give an outline of how responses are obtained and how their characteristics are measured, together with several sample applications, ranging from operating room monitoring to urology. There is also a section on safety with a concluding section of references.

Motor Evoked Potentials (MEPs)

Magnetically evoked motor potentials can be obtained by stimulating neural tissue such as the motor cortex, spinal nerve roots and peripheral nerves. Responses can be recorded in the normal manner using Electromyograpgic (EMG) or evoked potential equipment. In the case of muscle action potentials (MAP), averaging is not generally necessary because of the size of the response. Depending on the response size, nerve action potentials (NAP) may require averaging. Using a more accurate figure of eight coil, the Magstim 200^2 can be used to measure the peripheral motor nerve conduction velocity (PNCV).

The technique of magnetic stimulation is superior to conventional electrical stimulation in the stimulation of deep and less accessible nerves. Responses are quick to obtain without needing stimulation site preparation. Motor evoked potentials from the Abductor Digiti Minimi (ADM) in response to magnetic stimulation of wrist, elbow, Erbs point, cervical spinal root and the motor cortex are shown in Figure 26. Measurements available from the waveforms will include conduction latency, response amplitude (either base-line to first peak, or peak to peak value), and the threshold of stimulation. Other parameters also noted, which are perhaps used less frequently, include morphology (number of response phases), response area, power spectrum, silent period, fatigue and central recovery time.

In the example shown, the latency of each stimulation is marked; note that the amplitude scale varies each time, indicating the variable EMG amplitude generated for each stimulation.

Facilitation

With central nervous system responses it is possible to reduce the stimulation threshold by approximately 25%, increase the response amplitude 2-5 times and reduce response latency by some 1-3ms through pre-activation of the target muscle (see Figure noting the changes in scales). This technique, referred to as facilitation, has been described in considerable detail by others [e.g. Rothwell et al. Review article. Exp Physiol 1991, 76: 159-200]. Where the patient is able to contract the target muscle, the clinician can reduce the power level resulting in increased patient comfort. A facilitatory pulse (see: pulse pairs) will obtain a patient non-volitional response. Tables of normal data are available for both relaxed and facilitated muscles, [Mills KR. *Magnetic Stimulation of the Human Nervous System*, Oxford University Press, Book, (ISBN 0 19 262986 7), 1999; pages 174-176]. The measurement of conduction latency with facilitation requires several superimposed responses to determine the exact take-off point.

MEP Variability

Responses to peripheral stimulation are accurately repeatable. With cortical magnetic stimulation a considerable amount of response variability has been noted. Initially these were thought to result from variations in application techniques. Careful experiments have shown this variability to be a neurological phenomenon which results from continually changing excitability of the cortex. Measurement of this variability may prove clinically useful in certain disorders. However, the MEP variability can be overcome by using the triple stimulation technique described by Magistris et al. (1999). The triple stimulation technique links central to peripheral conduction through a collision technique which suppresses desynchronisation of the motor evoked potentials (MEP's), and is thus a very reliable and sensitive method for evaluating central motor conduction failures. [Magistris MR, Rosler KM, Truffert A, Landis T, Hess CW. *A clinical study of motor evoked potentials using a triple stimulation technique.* Brain, 1999; 122: 265-279].

Central Motor Conduction Time (CMCT)

An example of the measurement of CMCT is given below:

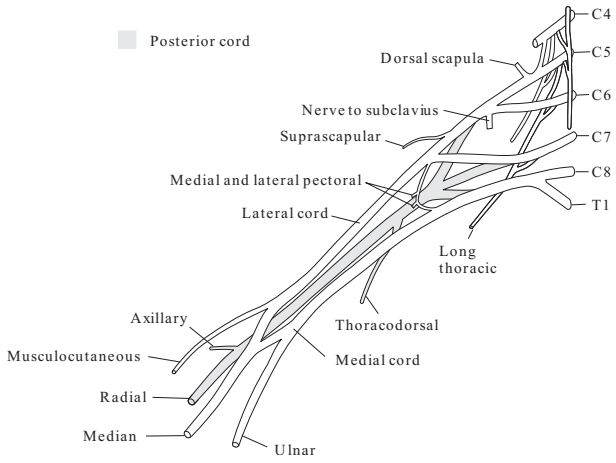


Figure 27: diagrammatic view of the brachial plexus and associated cervical nerve roots

Figure 27 illustrates the complexity of the brachial plexus. By choosing particular muscles, it is possible to measure CMCT times to C5, C6, C7 or C8. In this example the Abductor Digiti Minimi (ADM) muscle was utilised, the innervation for this muscle arising from the C8 nerve root (Figures 27and 28).

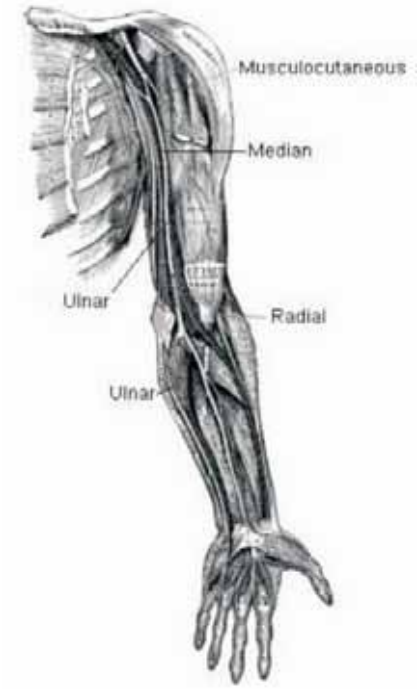


Figure 28: view of the upper limb showing major nerves and their general muscle innervation

The skin in the area of the ADM and Tibialis Anterior (TA) was cleaned by washing with an alcohol wipe, and surface type electrodes attached (Kendall ARBO monitoring electrodes); screened EMG wires were attached and connected to a Neurosign 400 EMG monitor; 2 channels were used (either upper limbs or lower limbs). A Magstim 200^2 single pulse, monophasic magnetic stimulator was used to evoke the response.

The cortical response was determined first, using a 90mm circular coil with a peak output of 2T. The coil was positioned with its centre over the vertex, the diameter of the coil being such that the part of the motor cortex controlling the upper limbs is stimulated with the coil in this position. With side B showing, the left side was stimulated, and with the A side showing, the right side was stimulated, at a power of 40%. This reference to Side A or Side B refers to the direction in which the current in the coil is flowing; relative to the patient's head, the current will flow in the opposite direction if the coil is turned over. As the motor cortex is sensitive to the direction of current flow, from posterior to anterior, it matters which way up the circular coil is positioned - hence side A and side B.

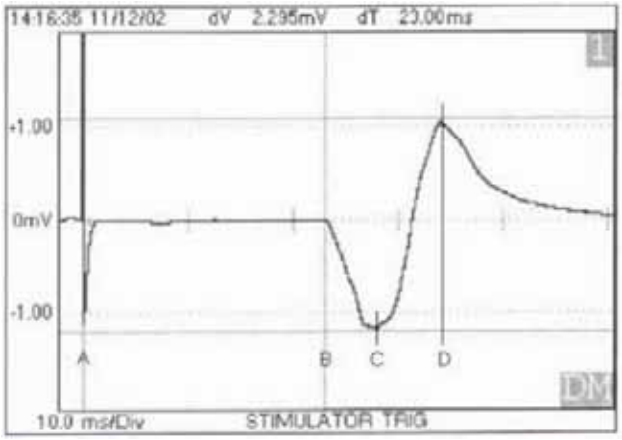


Figure 29: Cortical magnetic stimulation of the upper limbs; recording electrodes positioned on Abductor Digiti Minimi (ADM); the large spike at A is stimulus artifact; latency is 23ms as measured at B (δT); C and D are the minimum and maximum values of the EMG in mV, given by δV at the top of the screen (2.295mV)

Latencies of 23ms for the left side and 24.2ms for the right side were established. Figure 29 shows the EMG waveform of the left side stimulation; A is the point of stimulation, showing the large artifact spike generated by the discharge current, which caused electrical noise detected by the electrodes; B is the point at which the EMG deflection starts, and represents the first muscle fibres contracting. Points C and D represent the minimum and

maximum values of the EMG voltage, in this case 2.295mV. B - A represents the latency, in this case 23ms.

Stimulation at C7/T1 was performed next. Using the double 70mm 'figure of eight' coil, the coil was positioned with its centre 1.5cm to 2cm to the left of the midline of the spinal column at the C7/T1 level, with the coil handle at an angle of 45° to the vertical and pressed firmly into the patient, with the patient holding their head forward so as to present as straight a line as possible. Stimulation of the right side involves moving the coil 1.5cm to 2cm to the right of the midline of the spinal column. The power output of the stimulator was set to 65%. Latencies of 14.8ms for the left side and 15.2ms for the right were established.

The CMCT is given by the difference between the cortical latency and the peripheral latency; left side is 23-14.8 = 8.2ms and for the right is 24.2-15.2 = 9.0ms for the Central Motor Time from cortex to the C7/T1 cervical nerve root. There is a trans-synaptic period of approximately 1ms, leading to a CMCT of 7.2 - 8ms.

To include the spinal cord to L4/L5 in the CMCT measurement, Tibialis Anterior (TA) is used as the target muscle. The EMG cables were transferred to the TA electrodes, and the subject stimulated using the Double Cone Coil. This coil is designed to stimulate deeper into the motor cortex but also uses the 'butterfly' design, so is more accurate and success is more dependent on coil placement. Using a power output of 50%, with the coil slightly forward of the vertex and 1cm to the contralateral side of the midline, cortical latencies of 33.2ms for the left side and 32.6ms for the right side were recorded.

TA is largely innervated by L4; the double 70mm coil was used at 80% to stimulate the L4/L5 spinal roots. By careful placement of the coil, it is possible to stimulate the left or right nerve root; by altering the vertical position of the coil, the maximal amplitude of the response indicating the correct level. To be more precise, electrodes could also be attached to the peroneus longus muscle, innervated by L5. By stimulating and looking where the response changes from peroneus longus to tibialis anterior, the correct level can be established. The latency was recorded as 14ms for the left side, and 14.4ms for the right.

The CMCT including the spinal cord is therefore 33.2-14 = 19.2ms for the left side and 32.6-14.4 = 18.2ms for the right side. The results are summarised in Table 2.

The speed of conduction along the peripheral portion of a nerve can also be calculated. The subject was measured from C7 to ADM (0.87m); the latency was an average of 15ms; therefore the conduction velocity is given by:

$$v_{cond} = \frac{(L_{C7} - ADM)}{L_t} = \frac{0.87m}{0.015s} = 58m/s$$

where v_{cond} is conduction velocity and L is latency. As the length between C7 and ADM can only be approximated, there is inevitably some error built into this equation.

Measurement	Left	Right
Conduction time C7/T1 to ADM (ms)	14.8	15.2
Conduction time motor cortex to ADM (ms)	23	24.2
CMCT (ms) [cortex to C7/T1]	7.2	8.0
Conduction time L4/5 to TA (ms)	14	14.14
Conduction time motor cortex to TA (ms)	33.2	32.6
CMCT (ms) [cortex to L4/L5]	**18.2**	**17.2**

Table 2: summary of measurements made on a single subject to illustrate CMCT calculation

Note that in Table 2, a 1ms trans-synaptic delay has been subtracted from the raw CMCT value.

From the patient's perspective, the most important feature of magnetic stimulation is that it is painless [Barker et al, 1987]; because the magnetic field can pass unhindered through clothing, skin and bone (although there is evidence that in some skeletal structures such as the vertebrae, the magnetic field induces currents which flow round the circular portion of the bone and so concentrate at the foramina, and conversely make it difficult to stimulate the spinal cord), it is also the only practical method of stimulating the brain in an awake subject. Magnetic stimulation has, therefore, been widely used in University and Medical Research institutions to study the function of the brain [Barker et al, 1987].

The CMCT is abnormal in many disorders of the nervous system and, together with the other parameters measured, forms the basis for diagnosis and assessment. There are numerous normative and patient data available for many

human muscles or, if required, users can create their own tables of data to suit their own circumstances. Typically if the CMCT is outside the mean plus two standard deviations, the conduction is considered abnormal.

Corticomotor Threshold

The threshold of stimulation is a sensitive indicator of abnormality in certain disorders, especially where CMCT, when measured, can be normal, as in stroke (tests for this disorder are described later). Threshold can be defined as the power level at which a response can be detected 50% of the time, and it can be measured for both facilitated and relaxed muscles. Due to variable responses, it is necessary to repeat the stimulation several times - three responses out of six stimuli has been suggested as a standard. Measurement of the threshold of stimulation in disorders of the central nervous system has the advantage of reduced power levels and no peripheral stimulation. Its repeatability and comfort eases longer term assessment, for example in rehabilitation and drug therapy monitoring.

Response amplitude

A supra maximal stimulus is generally a requirement with peripheral stimulation. It is not possible to evoke a supra maximal response by cortical stimulation and the amplitude tends to be noted singularly, or as a ratio of supra maximal peripheral response. In normal subjects this ratio is above 50% for facilitated hand muscles but can be 5% or less in several disorders such as stroke and multiple sclerosis.

Limitations

It has not yet proved possible to stimulate the spinal cord itself. It is thought that the bone and cartilage surrounding the cord impedes inwards current flow from the outside, and that the spinal cavity itself does not have a large enough area to allow sufficient induced current. Cortical and spinal root stimulation, however, overcome this limitation in most clinical uses (as an example see section on cervical spondylosis).

Demyelinating Neuropathies

While the Double 25mm Coil does not replace all the standard MCV and SNCV tests, magnetic stimulation has become as reliable as conventional electroneurography in the assessment of some demyelinating neuropathies. With less discomfort and a shorter examination time, magnetic stimulation is of particular use in the non-invasive stimulation of deep nerves, and especially spinal nerve roots such as the phrenic nerve where electrical stimulation is both very painful and sometimes unreliable.

Magnetic Pulse Pairs

Magnetic Pulse Pairs with a timed stimulus interval can be effected either through a single coil or through two independent coils. This allows the study of central motor facilitatory and inhibitory phenomena, and the measurement of the recovery time of the central motor system. The study of the post excitatory silent period adds useful information in the assessment of Parkinson's, motor neurone disease etc, and pulse pairs can also assess the suitability of drug therapies for various conditions such as epilepsy. The use of a conditioning pulse produces a non-volitional facilitatory and quantifiable MEP response when used in paediatrics, in the assessment of stroke and similar studies.

Brain Mapping

The use of a figure eight coil with appropriate orientation permits a more defined stimulus to be given to the motor cortex. This in turn allows for topographical brain maps to be produced which can be of great value in the study of corticomotor projections in the underlying motor cortex. Brain mapping studies allow the monitoring of plasticity in the organisation of the motor cortex across a range of pathological and experimental conditions.

Sensory Evoked Potentials (SEPs)

Magnetic stimulation can also be used to stimulate sensory nerve fibres. The response can be recorded over sensory nerves and averaged in the normal manner. The advantage of magnetic stimulation over electrical is that of comfort. The disadvantage is the fact that stimulating coils may warm up before the end of the data acquisition. Magnetic sensory evoked potentials, so far relatively uncommon, are gaining popularity as coils improve and pulse repetition rates increase. A typical sensory response to magnetic stimulation at the wrist is shown in Figure 30. Owing to the small signal size, careful arrangement of recording electrodes is necessary to avoid stimulus artefact interference.

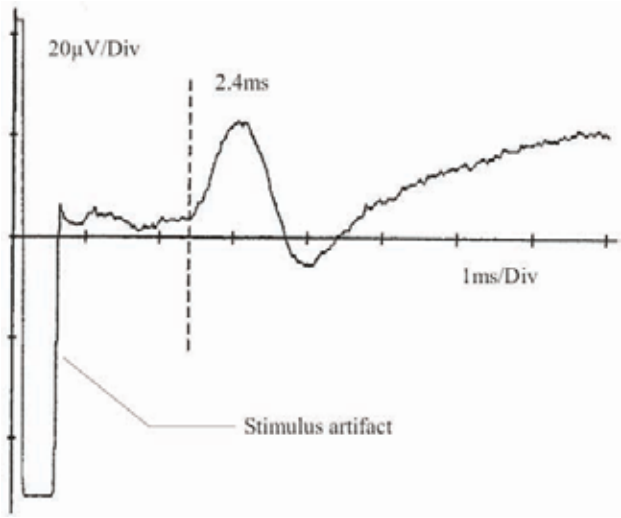


Figure 30: Responses from sensory nerves can also be recorded using magnetic stimulation. The averaged response (8 samples) shown above was recorded over the index finger after stimulation of the median nerve at the wrist using a double 25mm coil, with the stimulator set to 75% output power.

Sample Applications

The following sections listed alphabetically under their clinical headings provide a variety of sample applications covering peripheral, spinal nerve root and cortical stimulation. For further information on the sample applications and other areas not covered in this guide, the reader is referred to the 'Supplementary list of Reference Papers', available from the Magstim Company.

Coma

Transcranial magnetic stimulation gives clear evidence of valuable diagnostic and prognostic data in comatose patients, which allows for the early assessment of the pyramidal tract. Details of these procedures can be found in the following papers:

Chistyakov,A.V.; Soustiel,J.F.; Hafner,H.; Trubnik,M.; Levy,G.; Feinsod M. *Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury.* J.Neurol. Neurosurg. Psychiat. 2001; 70 (5): 580-587

Firching R. *Clinical applications of magnetic TCS in comatose patients. In: Clinical Applications of Magnetic Stimulation.* Lissons MA (Ed.) Peeters Press, Belgium, 1992; 263-268

Rohde V, Irle S, Hassler WE. *Prediction of the post-comatose motor function by motor evoked potentials obtained in the acute phase of traumatic and non-traumatic coma.* Acta Neurochirurgica, 1999; 141 (8): 841-848

Drug Monitoring

The effect of drugs on corticomotor excitability can be measured using twin pulse TMS. The threshold of stimulation may be raised or lowered; silent period may be shortened or lengthened; intracortical inhibition may be increased or decreased; intracortical facilitation may be increased or decreased. Many clinics worldwide find this a very useful method for an early assessment of how an individual reacts to a drug. If a drug does not appear to be having the desired effect on a patient, this can be detected early and the drug changed for a more effective alternative.

Rizzo V, Quartarone A, Bagnato S, Battaglia F, Majorana G Girlanda P. *Modification of cortical excitability induced by gabapentin: a study by transcranial magnetic stimulation.* Neurological Sciences, 2001, Vol 22, Iss 3, pp 229-232

Schulze-Bonhage, Knott K, Ferbert A. *Effects of carbamezepine on cortical excitatory and inhibitory phenomena: a study with paired transcranial magnetic stimulation.* Electroencephalography and Clin Neurophysiol, 1996;99:267-273

Werhahn KJ, Fordereuther S, Straube A. *Effects of serotonin (1B/1D) receptor agonist zolmitriptan on motor cortical excitability in humans.* Neurology, 1998; 51 (3): 896-898

Ziemann U, Tergau F, Bruns D, Baudewig J, Paulus W. *Changes in human motor cortex excitability induced by dopaminergic and anti-dopaminergic drugs.* Electroencephalography and Clinical Neurophysiology, 1997; 105: 430-7

Epilepsy

Techniques have evolved for monitoring the ôeffects of anti-epileptic drugs on motor cortex excitability in humans (A TMS study. Ziemann U et al. Annals of Neurology,1996;40:367-378).

Recent research papers report trials in which the number of seizures in some epileptic patients have been reduced following the application of repetitive transcranial magnetic stimulation, though results to date do not appear to be long lasting.

Cantello R. *Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy.* Neurology, 2002, Vol 58, Iss 7, pp 1135

Tergau F, Naumann U, Paulus W, Steinhoff BJ. *Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy.* Lancet, 1999; 353 (9171): 121-123

Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, Werhahn K, Kelley KR, Cohen L. *Transcranial magnetic stimulation for the treatment of seizures.* Neurology, 2002; 59: 560-562

Ziemann U, Lnnecker S, Steinhoff BJ, Paulus W. *Effects of Antiepileptic Drugs on Motor Cortex Excitability in Humans: A Transcranial Magnetic Stimulation Study.* Annals of Neurology, 1996;40:367-378

Facial Nerve

Magnetic stimulation has been used for across-the-lesion testing of facial nerve function. It complements MRI by looking at the function instead of the anatomy of the nerve. Both cortical and peripheral motor areas as well as the intracranial part of the facial nerve can be assessed. Coil positioning for peripheral stimulation of the facial nerve and typical responses are shown in Figure 31 using the circular 50mm coil (see Table 1). The actual site of peripheral nerve stimulation was shown to be in the labyrinthine segment of the facial canal [Rosler et al. EEG, 1991, Suppl 43: 362-368].

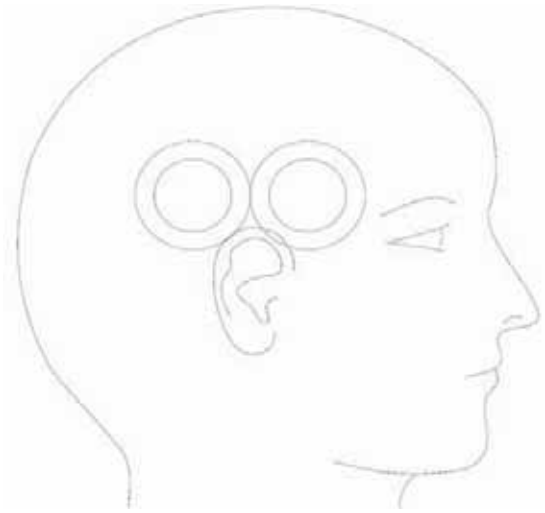


Figure 31: 50mm double coil positioned to stimulate the facial nerve in the labyrinthine segment of the facial canal

Figure 33 shows the latency of peripheral stimulation as 4.05ms for this subject; for the same subject, Figures 32 and 34 show the cortical latency without and with facilitation. Note that the latency has reduced by 2.7ms.

Cortical stimulation can be achieved through the use of the same coil placed over the contra lateral motor cortex, allowing the calculation of the central motor conduction time. In this particular subject, the CMCT using the facial muscles was 12.85 - 4.85ms = 8ms; however, as the peripheral stimulation takes place in the labyrinthine segment

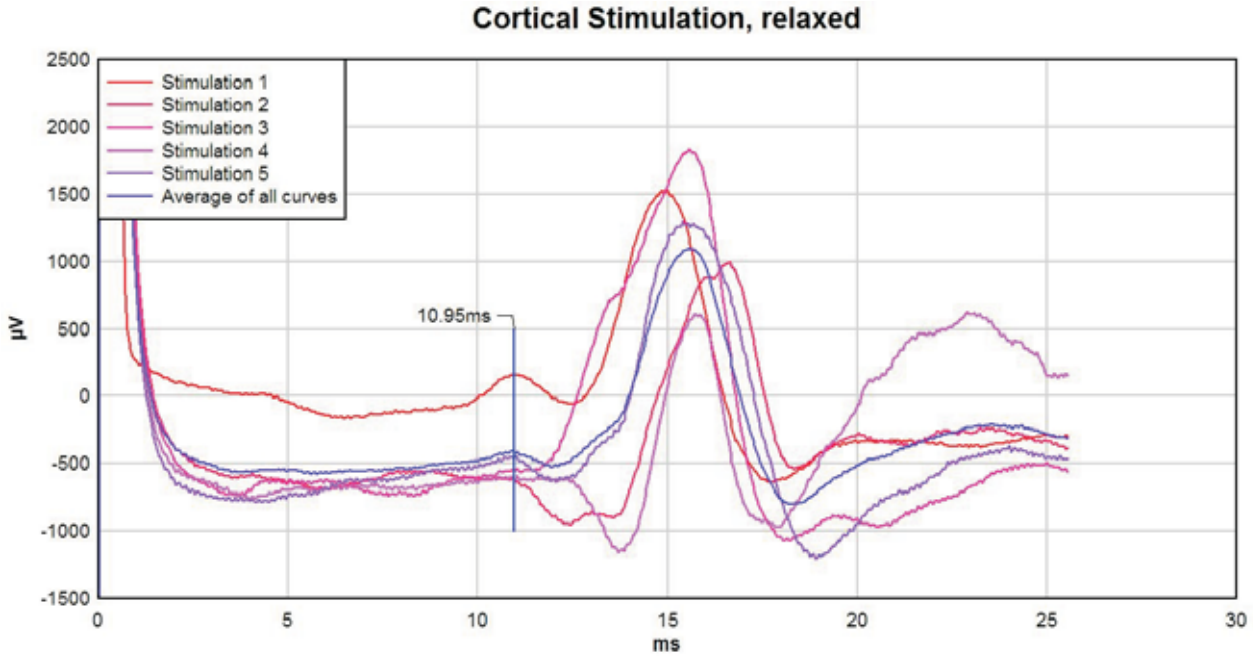


Figure 32: cortical stimulation of the facial motor cortex with the facial muscles relaxed

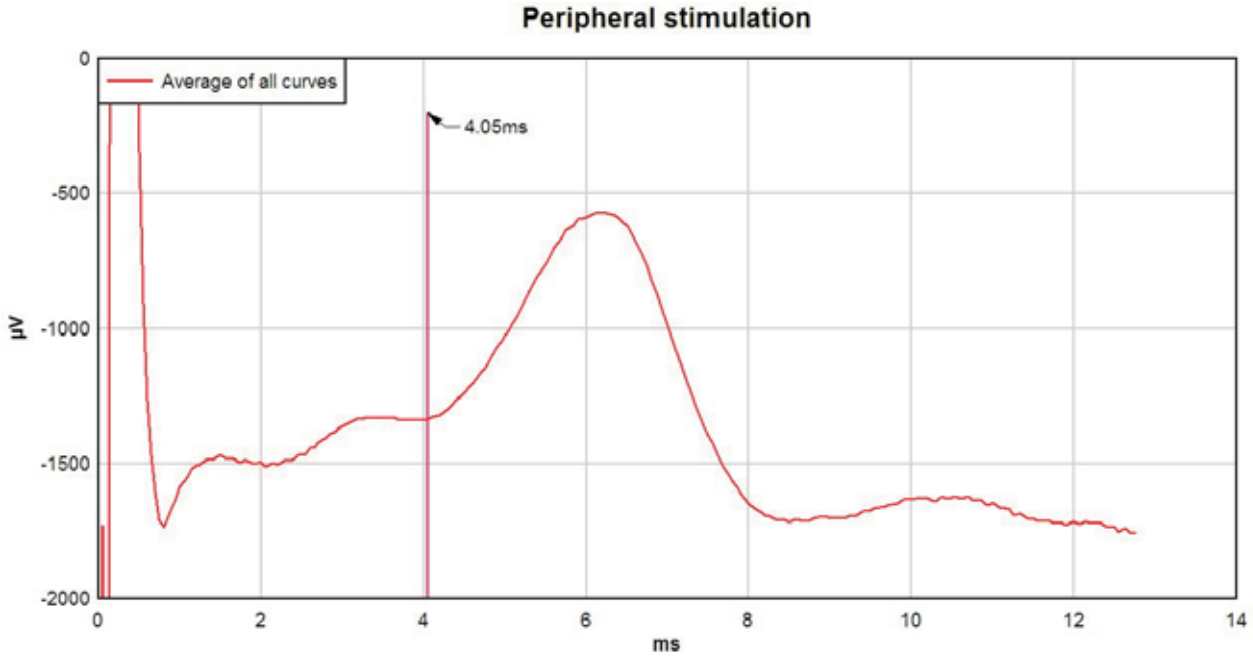


Figure 33: peripheral facial nerve stimulation with a double 50mm coil and electrodes located on mentalis

of the facial canal, there is a significant length of 'peripheral' nerve leading back to the brainstem, and since part of this is unmyelinated, and hence relatively slow conducting, this value for CMCT is over-estimated.

This method makes it possible to assess the motor routes to the facial muscles over distinct segments and to provide evidence of facial nerve lesions located in the facial canal at an early stage, such as in Bell's Palsy. Magnetic stimulation applied early after the onset of Bell's Palsy can indicate patients in whom recovery is likely to be good but it cannot identify patients whose recovery is likely to be poor. Transcranial and extracranial stimulation of the trigeminal, hypoglossal and accessory motor pathways is possible but results

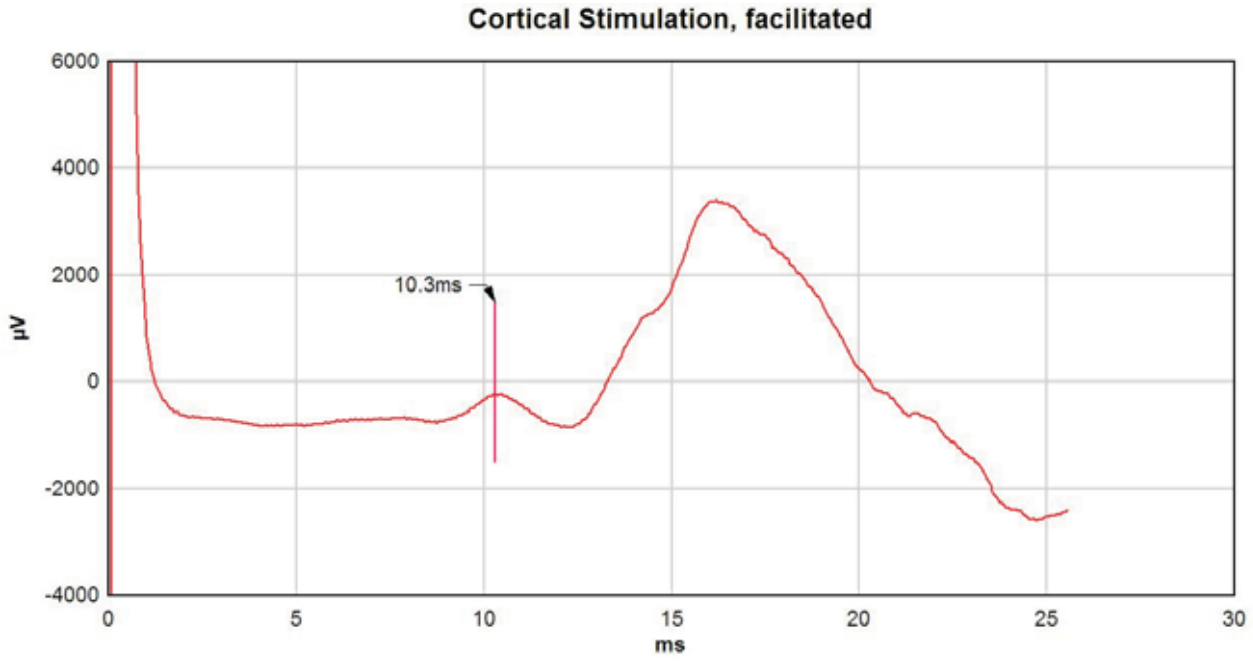


Figure 34: cortical stimulation of the facial motor cortex with slight facilitation - note the decreased latency

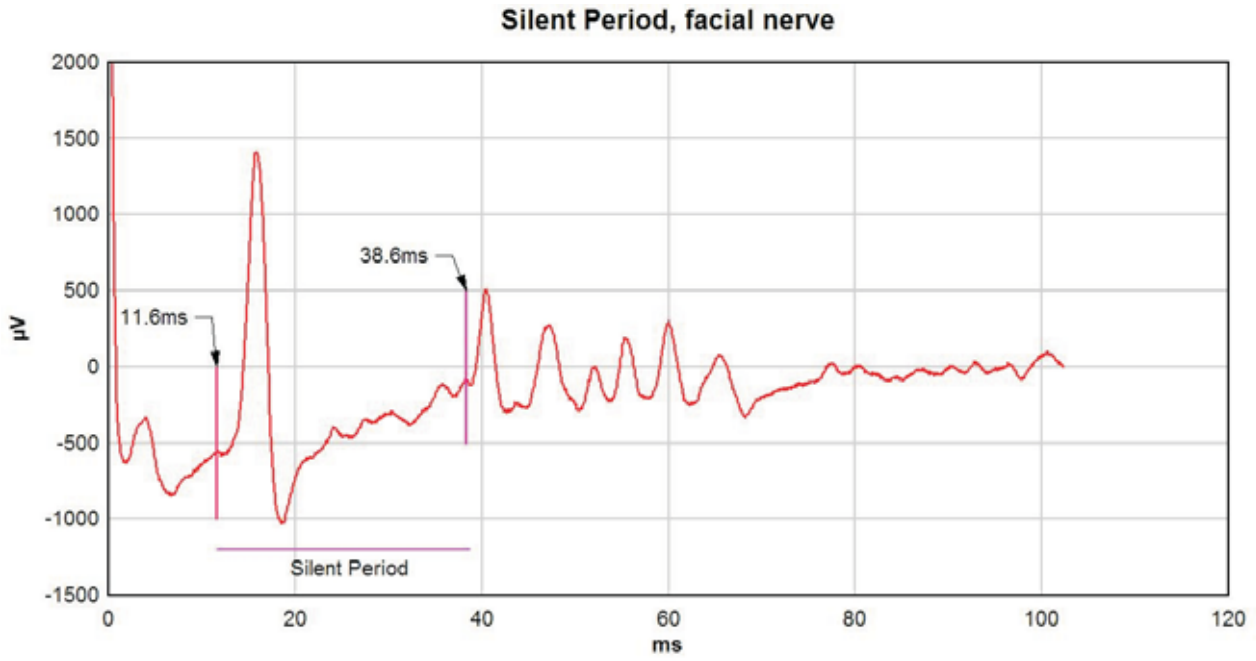


Figure 35: cortical stimulation of the facial motor cortex, showing initial EMG response followed by silent period and secondary EMG; Magstim 200^2, single pulse at 70% output and double 50mm coil

are not always easy to evaluate owing to cross muscle contamination.

Cocito A, Isoardo G, Migharetti G, Ciaramitaro P, Rota E, Poglio F, Bergamasco B. *Intracranial stimulation of the facial nerve: normative values with magnetic coil in 240 nerves.* Neurological Sciences, 2003; 23(6):307-311.

Glocker FX, Lucking CH. *Electrical and magnetic stimulation techniques for the diagnosis of facial nerve palsy and hemifacial spasm.* Klinische Neurophysiologie, 1998; 29(2): 59-65. (German)

Har-El G, McPhee JR. *Transcranial magnetic stimulation in acute facial nerve injury.* The Laryngoscope, 2000; 110: 1105-1111.

Hopf HC, Glocker FX. *Treatment of the idiopathic peripheral facial paresis (Bell's palsy)* Aktuelle Neurologie, 2001, Vol 28, Iss 9, pp 421-42.

Kotterba S, Tegenthoff M, Malin JP. *Hemifacial spasm or somatoform disorder - postexcitatory inhibition after transcranial magnetic stimulation as a diagnostic tool.* Acta Neurol Scand. 2000; 101: 305-310.

Psillas G, Daniilidis J. *Facial electroneurography on the contra lateral side in unilateral Bell's palsy.* European Archives of Oto-Rhino-Laryngology, 2002, 259(6):339-342

Urban PP. *Transcranial magnetic stimulation (TMS) in brainstem lesions and lesions of the peripheral cranial nerves.* Klinische Neurophysiologie, 2003, 34(1): 21-31

Vogt T. *Myokymias of the face and facial spasm.* Klinische Neurophysiologie, 2002; 33,17-24

Spinal nerve roots

Magnetic stimulation provides a simple and painless means of stimulating spinal nerve roots. As the point of stimulation is known to be the exit of the foramina, the conduction times to target muscles can be compared with normal values, and this can then confirm or lead to a diagnosis, and over time can plot the course of the disease or recovery of the patient. Because it is painless, it becomes feasible to repeat the conduction time measurements on a regular basis - the patient is much more likely to come back! In comparison, electrical stimulation of spinal nerve roots involves inserting a needle close to the nerve root, then passing a current through the needle. This can be painful, not just because of the needle insertion, but also because the electrical stimulation is likely to stimulate pain fibres within the nerve bundle - the magnetic pulse of 100s is too short.

By using the 90mm circular coil, the nerve roots on both sides can be stimulated together. As the coil has a relatively large magnetic field, it is very likely

that more than a single vertebral level will be stimulated (See Figure 38).

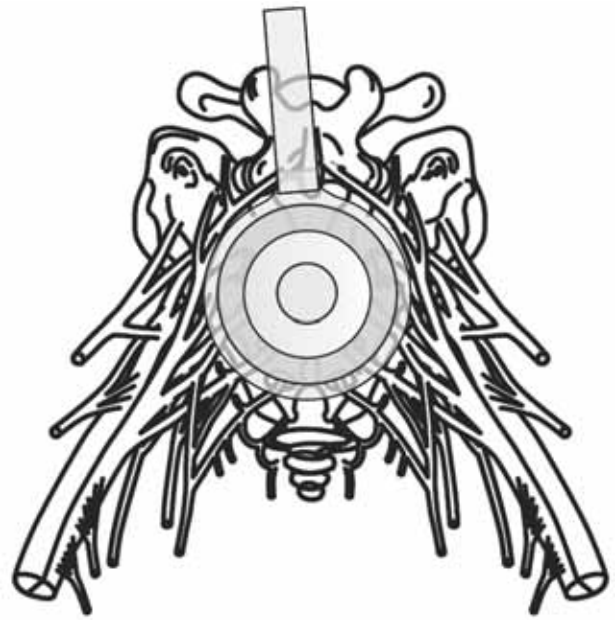


Figure 38: the 90mm coil placed over the sacrum, showing that a number of nerve roots are likely to be stimulated

In contrast, the double 70mm coil has a much more defined magnetic field, with the two coil windings summating under the centre of the coil. This provides a sharp peak to the magnetic field, and this coil can be used to stimulate a single nerve root on one side. It requires more practice to

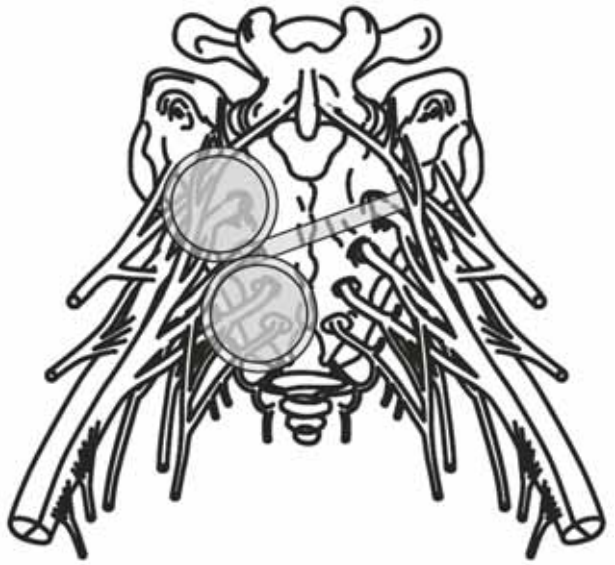


Figure 36: the double 70mm coil placed over the sacrum. The peak magnetic field is where the 2 windings meet - hence accurate stimulation is possible

find the nerve root, and it is important to ensure that the relevant target muscle group is being monitored for EMG activity (see Figure 36). We are all individual, and the vertebral level which provides major innervation for tibialis anterior in one person may provide innervation for quadriceps in another.

The user must determine the balance between ease of stimulation, clinical need and patient comfort when deciding which coil to use.

Figure 37 shows the EMG waveform of the medial head of the gastrocnemius muscle when stimulated at the S1 nerve root. The latency is c.14ms, and a double 70mm coil was used.

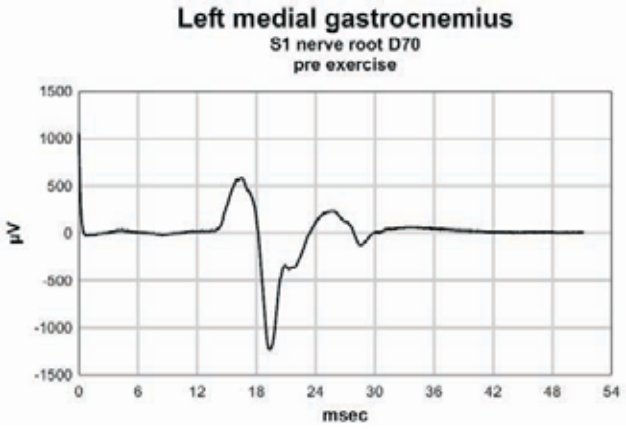


Figure 37: stimulation of S1 nerve root and resultant EMG from medial gastrocmenius muscle; normal trace from healthy 47 year old male

T1 - T12	Chest wall appropriate with level
L3	Adductors
L4	Quadriceps
L5	Peroneus longus
S1	Medial gastrocnemius
S2 - S3	Perineum
S4 - S5	Adductor hallucis, plantar muscles of foot; buttocks

Table 3: some suggested muscle sites for specific vertebral levels

Motor Neurone Disease

Electrophysiological evaluation and monitoring is of vital importance in amyotrophic lateral sclerosis in helping to assess the severity of the disease and to monitor the rate of its progression. Transcranial magnetic stimulation is proving to be a most sensitive tool for the assessment of upper motor neurone involvement, besides its ability to monitor changes in stimulation threshold, silent

period duration, cortical excitability and respiratory muscle involvement. Further reading should include:

Attarian S, Azulay J Ph, Pouget JY. *Transcranial magnetic stimulation is a sensitive tool to evaluate upper motor neuron dysfunction in ALS.* Neurology, 2000; 54 (7-3): S68-002

Eisen A. *Clinical electrophysiology of the upper and lower motor neurone in amyothrophic lateral sclerosis.* Seminars in Neurology, 2001; 21 (2): 141-154

Hanajima R, Ugawa Y. *Impaired motor cortex inhibition in patients with ALS: evidence from paired transcranial magnetic stimulation.* Neurology, 1998; 51 (6): 1771

Polkey MI, Lyall RA, Green M, Leigh PN, Moxham J. *Expiratory muscle function in amyotrophic lateral sclerosis.* American Journal of Respiratory and Critical Care Medicine, 1998;158 (3):734-741

Pouget J, Trefouret S, Attarian S. *Transcranial magnetic stimulation (TMS): compared sensitivity of different motor response parameters in ALS.* Amyotrophic Lateral Sclerosis and Other Motor Neurone Disorders, 2000; 1 (2): S45-S49.

Salerno A, Georgesco M. *Double magnetic stimulation of the motor cortex in amyotrophic lateral sclerosis.* Electroenceph. clin. Neurophysiol., 1998;107:133-139

Similowski T, Attali V, Bensimon G, et al. *Diaphragmatic dysfunction and dyspnoea in amyotrophic sclerosis.* European Respiratory Journal, 2000; 15 (2): 332-337.

Triggs WJ, Menkes D, Onorato J, Yan RSH, Young MS, Newell E, Sander HW, Soto O, Chiappa KH Cross D. *Transcranial magnetic stimulation identifies upper motor neurone involvement in motor neuron disease.* Neurology, 1999; 53 (3): 605-611.

Ziemann U, Winter M, Reimers CD, Reimers K, Tergau F, Paulus W. *Impaired Motor cortex inhibition in patients with amyotrophic lateral sclerosis - Evidence from paired transcranial magnetic stimulation.* Neurology, 1997; 49: 1292-1298

Movement Disorders

Abnormalities of motor control not attributable to lesions of the pyramidal tract are listed in this section. The list is not meant to be comprehensive but to cover those diseases which have been researched using transcranial magnetic stimulation.

Numerous TMS studies of movement disorders have provided a wealth of clinical information about Huntington's Chorea, Focal Dystonia, Cortical Myoclonus, Parkinson's Disease, Essential Tremor, Wilson's Disease etc., while some have indicated that there may also be therapeutic benefits in some conditions such as Parkinson's disease. Double pulse stimulation techniques also allow for the monitoring of other therapeutic effects upon movement disorders such as drug treatment or surgery.

Floeter MK, Rothwell JC. *Releasing the brakes before pressing the gas pedal.* Neurology, 1999; 53: 664-665

Dystonia

Motor evoked potentials have normal threshold responses in patients with dystonia but central motor conduction studies may detect subtle abnormalities in response to TMS. Patients with focal dystonia show a greater amplitude of facilitated muscle response when compared to normal subjects and their silent period is often shorter. Paired pulse stimulation at short interstimulus intervals (1-5ms) reveals reduced inhibitory effect (Ridding et. al 1995b).

Abbruzzese G, Marchese R, Buccolieri A, Gasparetto B, Trompetto C. *Abnormalities of sensorimotor integration in focal dystonia - A transcranial magnetic stimulation study.* Brain, 2001; 124 (3): 537-545.

Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. *The pathophysiology of primary dystonia.* Brain, 1998; 121 (7): 1195-1212

Curra A, Romaniello A, Berardelli A, Cruccu G, Manfredi M. *Shortened cortical silent period in facial muscles of patients with cranial dystonia.* Neurology, 2000; 54 (1): 130-135

Gilio F, Curra A Lorenzano C Modugno N, Manfredi M, Berardelli A. *Effects of botulinum toxin type A on intracortical inhibition in patients with dystonia.* Annals of Neurology, 2000; 48 (1), 20-26

Kanovsky P, Streitova H, Dufek J, Znojil V, Daniel P, Rektor I. *Lateralization of the P22/N30 precentral cortical component of the median nerve somatosensory evoked potentials is different in patients with a tonic or tremulous form of cervical dystonia.* Movement Disorders, 1999; 14 (4): 642-651

Meyer BU, Irlbacher K, Meierkord H. *Analysis of stimuli triggering attacks of paroxysmal dystonia induced by exertion.* Journal of Neurology, Neurosurgery and Psychology, 2001; 70 (2): 247-251

Mills KR. *Magnetic stimulation of the human nervous system.* Oxford University Press, 1999; 265

Ridding MC, Sheean G, Rothwell JR, Inzelberg R, Kujirai T. *Changes in the balance between motor-cortical excitation and inhibition in focal, task specific dystonia.* J. Neurol. Neurosurg. Psychiatry, 1995b; 59: 493-498

Rona S, Berardelli A, Vacca L, Inghillaeri M, Manfredi M. *Alterations of motor cortical inhibition in patients with dystonia.* Movement Disorders,1998;13:118-124

Schwenkreis P, Vorgerd M, Malin JP, Tegenthoff M. *Assessment of postexcitatory inhibition in patients with focal dystonia.* Acta Neurologica Scandinavica, 1999; 100 (4): 260-264

Sommer M, Ruge D, Tergau F, Beuche W, Altenmuller E, Paulus W. *Intracortical excitability in the hand motor representation in hand dystonia and blepharospasm.* Movement Disorders, 2002, Vol 17, Iss 5, pp 1017-1025

Thickbroom GW, Byrnes ML, Stell R, Mastaglia FL. *Reversible reorganisation of the motor cortical representation of the hand in cervical dystonia.* Movement Disorders, 2003; 18 (4): 395-402

Huntington's Disease

Studies of Huntington's Disease have found modest abnormalities of central motor conduction including latency variability, with a moderately increased motor threshold in some patients. There might also be a lengthened silent period.

Abbruzzese G, Marchese R, Trompetto C. *Motor cortical excitability in Huntington's disease.* Journal of Neurology, Neurosurgery and Psychiatry, 2000; 68 (1): 120

Abbruzzese G, Buccolieri A, Marchese R, Trompetto C, Mandich P, Schieppati M. *Intracortical inhibition and facilitation are abnormal in Huntington's disease: a paired magnetic stimulation study.* Neuroscience Letters, 1997a, 228; 87-90

Berardelli A. et al. *Pathophysiology of chorea and bradykynesia in Huntington's disease.* Movement Disorders, 1999; 14 (3): 398-403

Eisen AA, Bohlega S, Bloch M, Hayden M. *Silent periods, long latency reflexes and cortical MEPs in Huntington's disease and at risk relative.* Electroenceph and Clin Neurophys, 1989; 74: 444-449

Hmberg V, Lange WW. *Central motor conduction to hand and leg muscles in Huntington's disease.* Movement Disorders, 1990; 5 (3): 214-218

Meyer BU, Noth J, Herwig, et al. *Motor responses evoked by magnetic brain stimulation in Huntington's disease.* EEG and Clinical Neurophysiology, 1992; 84; 321-324

Meyer BU, Conrad B. *Neurophysiological and diagnostic application of transcranial brain stimulation in basal ganglia disorders In: Clinical Applications of Magnetic Stimulation.* Lissens M. A. (Ed.), Peeters Press, Belgium, 1992; 185-201

Mills KR, *Magnetic stimulation of the human nervous system.* Oxford University Press, 1999; 264-265

Priori A, Inghilleri M, Berardelli A. *Transcranial brain stimulation in basal ganglia diseases.* In Clinical Applications of Magnetic Stimulation. Lissons, M.A.(Ed.), Peeters Press, Belgium, 1992: 175-184

Priori A, Polidori L, Rona S, Manfredi M, Berardelli A. *Spinal and cortical inhibition in Huntington's chorea.* Movement Disorders, 2000; 15 (5): 938-946

Tegenthoff M, Vorgerd M, Juskowiak F, Roos V, Malin J.-P. *Postexcitatory inhibition after transcranial magnetic single and double brain stimulation in Huntington's disease.* Electroencephalogr Clin Neurophysiol, 1996;101:298-303

Vorgerd M. Tegenthoff M Juskowiak F. Roos V. Malin J-P. *Transcranial magnetic double stimulation: Methods and clinical studies.* Z. EEG-EMG, 1996;27: 85-91 (German with English Abstract)

Ziemann U, Koc J, Reimers CD, Finkenstaedt M, Paulus W. *Exploration of motor cortex excitability in a diabetic patient with hemiballism-hemichorea.* Movement Disorders, 2000; 15 (5): 1000-1005

Myoclonus

Cortical excitability, a shortened silent period and reduced inhibition have been revealed by some TMS studies as factors which allow the spread of myoclonic activity to motor cortical areas.

Brown P, Ridding MC, Werhahn KJ, Rothwell JC, Marsden CD. *Abnormalities of the balance between inhibition and excitation in the motor cortex of patients with cortical myoclonus.* Brain, 1996;119:309-317

Cantello R, Gianelli M, Civardi C, Mutani R. *Focal subcortical reflex myoclonus: A clinical and neurophysiological study.* Archives of Neurology,1997;54:187-196

Grosse P, Guerrini R, Parmeggiani L, Bonanni P, Pogosyan A, Brown P. *Abnormal corticomuscular and intermuscular coupling in high-frequency rhythmic myoclonus.* Brain, 2003; 126(2): 326-342

Guerrini R, Bonanni P, Parmeggiani L, Santucci M, Parmiggiani A, Sartucci F. *Cortical reflex myoclonus in Rett Syndrome.* Annals in Neurology, 1998; 43: 472-479

Kanouchi T, Yokata T, Kamata T, Ishii K, Senda M. *Central pathway of photic reflex myoclonus.* Journal of Neurology, Neurosurgery, and Psychiatry, 1997;62:414-417

Reutens DC, Puce A, Berkovic SF. *Cortical hyperexcitability in progressive myoclonus epilepsy.* Neurology, 1993;43:186-192

Rothwell JC, Brown P. *The spread of myoclonic activity through sensorimotor cortex in cortical reflex myoclonus.* Advances in Neurology, 1995; 67:143-155

Strafella A, Ashby P, Lang AE. *Reflex myoclonus in cortical-basal ganglionic degeneration involves a transcortical pathway*. Movement Disorders,1997;12:360-369

Tassinari CA, Rubboli G, Shibasaki H. *Neurophysiology of positive and negative myoclonus.* Electroencephalography and Clinical Neurophysiology, 1998; 107: 181-195

Parkinson's Disease

Since the onset of TMS, considerable attention has been given to the study of Parkinson's disease. The few papers shown below are only an example of what has been written and those with particular interest in this subject are recommended to read the selection in our 'Magnetic Stimulation Reference Papers by Subject' collated as a separate publication.

To date, TMS has proved to be a useful tool for the study and monitoring of pathophysiological mechanisms of Parkinson's disease as well as attracting attention as a possible therapeutic tool. However, a lot more study appears to be necessary before the latter becomes a reality!

Auer C, Mentschel C, Conrad B, Siebner HR. *Focal 5Hz repetitive transcranial magnetic stimulation of the primary motor hand area improves 'off' motor function in patients with Parkinson's disease.* Electroenceph. clin Neurophysiol,1998;107(3):91P

Berardelli A, Rothwell JC, Thompson PD, Hallet M. *Pathophysiology of bradykinesia in Parkinson's disease.* Brain, 2001; 124 (11): 2131-2146

Burn DJ. *Beyond the iron mask: Towards better recognition and treatment of depression associated with Parkinson's disease.* Movement Disorders, 2002; 17 (3): 445-454

Dioszeghy P, Hidasi E, Mechler F. *Study of motor functions using magnetic stimulation in Parkinson's disease.* Electromyogr Clin Neurophysiol, 1999; 39 (2): 101-5

Dragasevic N, Potrebic A, Damjanovic A, Stefanova E, Kostic VS. *Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: An open study.* Movement Disorders, 2002;17 (3): 528-532

Ellaway PH, Davey NJ, et al. *The relation between bradykynesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects.* Electroencephalogr Clin Neurophysiol, 1995;97:169-178

Filippi MM, Oliveri M, Pasqualetti P, Cicinelli P, Traversa R, Vernieri F, Palmieri MG, Rossini PM. *Effects of motor imagery on motor cortical output topography in Parkinson's disease.* Neurology, 2001; 57 (1) 55-61

Ghabra MB, Hallett M, Wassermann EM. *Simultaneous repetitive transcranial stimulation does not speed fine movements in PD.* Neurology, 1999; 52: 768-770

Gilio F, Curra A, Inghilleri M, Lorenzano C, Manfredi M, Berardelli A. *Repetitive magnetic stimulation of cortical motor areas in Parkinson's disease: Implications for the pathophysiology of cortical function.* Movement Disorders, 2002; 17 (3): 467-473

deGroot M, Hermann W, Steffen J, Wagner A, Grahmann F. *Contra lateral and ipsilateral repetitive transcranial magnetic stimulation in patients with Parkinson's disease.* Nervenarzt, 2001; 72 (12): 932-938

MacDonald V, Halliday GM. *Selective loss of pyramidal neurons in the pre-supplementary motor cortex in Parkinson's disease.* Movement Disorders, 2002; 17 (6): 1166-1173

Mally J, Stone TW. *Improvement in Parkinsonian symptoms after repetitive transcranial magnetic stimulation.* J Neurol Sci, 1999; 162 (2): 179-184

Mally J, Stone TW. *Therapeutic and ôdose-dependentö effect of repetitive microelectroshock induced by transcranial magnetic stimulation.* J Neurosci Res, 1999; 57 (6): 935-940

Marchese R, Trompetto C, Buccoliere A, Abbruzzese G. *Abnormalities of motor cortical excitability are not correllated with clinical features in atypical parkinsonism.* Movement Disorders, 2000; 15 (6): 1210-1214

Meunier S, Pol S, Houeto JL, Vidailhet M. *Abnormal reciprocal inhibition between antagonist muscles in Parkinson's disease.* Brain, 2000; 123 (5): 1017-1026

Mills KR. *Magnetic stimulation of the human nervous system.* Oxford University Press, 1999; 259-264

Okabe S, Ugawa Y, Kanazawa I. *0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease.* Movement Disorders, 2003; 18 (4): 382-388

Pascual-LeonP A, Alonso M, et al. *Lasting beneficial effects of rapid-rate transcranial stimulation on slowness in Parkinson's disease.* Neurology, 1995;45:550P, A315

VallsSole J, Tolosa E, Marti MJ, Valldeoriola F, Revilla M, Pastor P, Blesa R. *Examination of motor output pathways in patients with corticobasal ganglionic degeneration using transcranial magnetic stimulation.* Brain, 2001; 124 (6): 1131-1137

Von Raison F, Drouot X, Nguyen J-P, Cesaro P, Lefaucheur J-P. *The clinical effects of repetitive transcranial magnetic stimulation on Parkinson's disease depend on stimulation frequency.* Neurology, 2000; 54 (3): P04.043

Shimamoto H, Morimitsu H, Sugita S, Nakahara K Shigemori M. *Therapeautic effects of repetitive transcranial magnetic stimulation in Parkinson's disease.* Rinsho Shinkaigaku, 1999; 39: 1264-1267

Siebner HR, Mentschel C, Auer C, Conrad B. *Repetitive transcranial magnetic stimulation has a beneficial effect in bradykinesia in Parkinson's disease.* Neuroreport, 1999;0: 589-594

Young MS, Triggs WJ, Bowers D, Greer M, Friedman WA. *Stereotactic pallidotomy lengthens the transcranial magnetic cortical stimulation silent period in Parkinson's disease.* Neurology 1997:49:1278-1283

Tremor

TMS of the motor cortex can modulate the oscillatory mechanisms responsible for the generation of postural tremors (Britton et al. 1993).

Britton TC, Thompson PD, Day BL, Rothwell JC, Findley LJ, Marsden CD. *Modulation of postural wrist tremors by magnetic stimulation of the motor cortex in patients with Parkinson's disease or essential tremor and in normal subjects mimicking tremor.* Annals of Neurology, 1993; 33: 473-479

Mills KR, Nithi KA. *Motor cortex stimulation does not reset primary orthostatic tremor.* Journal of Neurology, Neurosurgery and Psychiatry, 1997; 63 (4): 553

Pascual-LeonP A, Valls-Solle J, et al. *Resetting of essential tremor and postural tremor in Parkinson's disease with transcranial magnetic stimulation.* Muscle and Nerve, 1994b; 17:800-807

Romeo S, Berardelli A, Pedace F, Inghillieri M, Giovanelli M, Manfredi M. *Cortical excitability in patients with essential tremor.* Muscle and Nerve, 1998; 21: 1304-1308

Tsai CH, Semmier JG, Kimber TE, Thickbroom G, Stell R, Mastaglia FL, Thompson PD. *Modulation of primary orthostatic tremor by magnetic stimulation over the motor cortex.* Journal of Neurology, Neurosurgery and Psychiatry,1998;64:33-36

Tourette Syndrome

Few TMS studies have been carried out on Tourette Syndrome but one found evidence of decreased motor inhibition (Ziemann et. al 1997). A later study by Mnchau et al. (2002), theorised that by using low frequency (1Hz) rTMS stimulation they may be able to tune down overactive cortical areas. The result of the trial did not show any significant difference after treatment. Reasons for an ineffective result may have been coil location (no brain imaging or neuronavigation guidance systems used), low intensity of stimulation at 80% of motor threshold. It is hoped that future studies will be forthcoming.

Munchau A, Bloem BR, Thilo KV, Trimble MR, Rothwell JC, Robertson M. *Repetitive transcranial magnetic stimulation for Tourette syndrome.* Neurology, 2002; 59 (11) 1789-1791

Ziemann U, Paulus W, Rothenberger A. *Decreased motor inhibition in Tourette's Disorder: Evidence from Transcranial Magnetic Stimulation.* The American Journal of Psychiatry,1997;154:1277-1284

Multiple Sclerosis

The quantification of motor disability in multiple sclerosis patients has been made possible by advances in magnetic stimulation techniques. The most important of these techniques are: threshold of response, minimal latency, central motor conduction time and response size in terms of amplitude, duration and area. Central motor conduction time (CMCT) studies can show a lengthening of latency times, indicating nerve demyelination, when imaging appears to be normal. Response size however, can only be accurately assessed by using the triple stimulation technique described by Magistris et al. (1999), as the amplitude of response shows a marked variability of response to cortical stimulation with

standard TMS techniques. The triple stimulation technique links central to peripheral conduction through a collision technique which suppresses desynchronisation of the motor evoked potentials (MEP's), and is thus a very reliable and sensitive method for evaluating central motor conduction failures.

Regular monitoring using these techniques can contribute to the patients quality of life by alerting the physician to the possibility of a pending relapse, thus allowing for the timely intervention of appropriate therapeutic drugs. Use of repetitive magnetic stimulation (rTMS), can be a useful therapeutic intervention in the cases of spasticity in MS. Studies undertaken by Nielsen et al. (1996) in a double-blind placebo-controlled trial, concluded that rTMS has an anti-spastic effect in MS. Similarly, trials conducted by Struppler et al. (1996) with stroke patients were successful in reducing spasticity. Struppler concluded, "We assume that also other forms of spastic paresis can be treated successfully or, in the early stages of central paresis, the development of spasticity could be prevented by immediate application of RPMS", (repetitive peripheral magnetic stimulation).

Boniface SJ, Schubert M, Mills KR. *Suppression and long latency excitation of single spinal motor neurones by transcranial magnetic stimulation in health, multiple sclerosis, and stroke.* Muscle and Nerve, 1994; 17:642-646

Brostrom S, Frederiksen JL, Jennum P, Lose G. *Motor evoked potentials from the pelvic floor in patients with multiple sclerosis.* Journal of Neurology Neurosurgery and Psychiatry, 2003; 74 (4):498-500

Dan B, Christiaens F, Christophe C, Dachy B. *Transcranial magnetic stimulation and other evoked potentials in pediatric multiple sclerosis.* Pediatric Neurology, 2000; 22 (2): 136-138

Fischer C, AndreObadia N, Mauguiere F. *Diagnostic criteria of multiple sclerosis: electrophysiological criteria.* Revue Neurologique, 2001, Vol 157, Iss 8-9, Part 2, pp 974-980

Kandler RH, Jarratt JA, Davies-Jones GA, Gumpert EJW, Sager HJ, Venables GS, Zeman A. *The role of magnetic stimulation as a quantifier of motor disability in patients with multiple sclerosis.* Journal of Neurological Sciences, 1991; 106: 25-30

Kidd D, Thompson PD, Day BL, Rothwell JC, Kendall BE, Thompson AJ, Marsden CD, McDonald WI. *Central motor conduction time in progressive multiple sclerosis - Correlations with MRI and disease activity*. Brain, 1998; 121: 1109-1116

Magistris MR, Rosler KM, Truffert A, Landis T, Hess CW. *A clinical study of motor evoked potentials using a triple stimulation technique.* Brain, 1999; 122: 265-279

Nielson JF. *Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study.* Multiple Sclerosis, 1996; 2:227-232

Nielson JF. *Frequency-dependent conduction delay of motor evoked potentials in multiple sclerosis.* Muscle & Nerve, 1997; 20:1264-1274

Nielson JF. *The role of transcranial magnetic stimulations and motor evoked potentials in the investigation of central motor pathways in multiple sclerosis.* Danish Medical Bulletin, 1996; 43:448-462

Schmierer K, Irlbacher K, Grosse P, Roricht S, Meyer BU. *Correlates of disability in multiple sclerosis detected by transcranial magnetic stimulation.* Neurology, 2002; 59 (8):1218-1224

Struppler A, Jakob C, Muller-Barna P, Schmid M, Lorenzen H-W, Paulig M, Prosiegal M. *New method for early rehabilitation in extreme palsies of central origin by magnetic stimulation.* Z. EEG-EMG, 1996;27: 151-157. German

Neuroscience

The principle of electromagnetic induction described by Michael Faraday in 1831 has been developed in the 20th century to produce a pulsed magnetic field, which in turn, induces an electrical current to flow in tissue when a stimulating coil is brought close to the site of stimulation. The magnetic field passes painlessly through bone and tissue and the induced electrical current activates cells or nerves in the area of focus. In turn this induced neuronal activity can mimic the effects of brain lesions, affect mood and elicit perceptions with a specificity that is remarkable in both space and time and with millisecond precision (Walsh 1998).

Since the first magnetic stimulators were manufactured in 1986, the gamut of life has been subject to magnetic stimulation, ranging from cell cultures through the animal kingdom to human studies. Through a variety of stimulating coils, transcranial magnetic stimulation enables the mammalian brain and descending and ascending peripheral tracts to be studied in relation to connectivity, including studies incorporating imaging such as MRI, fMRI or PET etc. The benign and painless nature of the induced

electrical currents and their ability to non-invasively and reversibly disrupt precise areas of the brain have enabled a wide area of cognitive and sensory functions to be studied, without causing any harm to its subjects. The many subjects studied include: cognition, neuronal facilitation and inhibition, mood, pain, plasticity, sleep, speech and visual cortex. Motor cortex mapping, investigation of descending tracts and integrity of motor pathways can also be evaluated.

Researchers are actively using differing protocols ranging from single pulse stimulation to look at brain connectivity, twin pulses to look at inhibitory and facilitatory circuits of the brain, and low frequency to high frequency stimulation to study longer lasting effects on brain activity and mood changes. Studies of migraine with aura, depression, schizophrenia, brain plasticity, spasticity during MS and post stroke, central fatigue etc. reveal potential benefits for clinical uses for TMS in Neurology, Neurophysiology, Rehabilitation, Sports Medicine, Psychology, and Psychiatry. TMS was listed as a priority area for primary research in HTA, December 1998, the NHS Research and Development Programme. Areas currently being researched in Psychiatry include obsessive compulsive disorders, mania, schizophrenia and depression.. Studies have produced a wealth of papers on a variety of subjects, some of which are listed below.

Chan P, Eng LF, Lee YL, Lin VW. *Effects of pulsed magnetic stimulation of GFAP levels in cultured astrocytes.* J. Neurosci Res, 1999; 55 (2): 238-244

DiLazzaro V, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, Saturno E, Pilato F, Masullo C, Rothwell JC. *Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation.* Neurology, 2002; 59 (3): 392-397

Edgley SA, Eyre JA, Lemon RN, Miller S. *Comparison of activation of corticospinal neurons and spinal motor neurons by magnetic and electrical transcranial stimulation in the lumbosacral cord of the anaesthetized monkey.* Brain,1997;120:839-853

Ellaway PH, Davet NJ, Ljubisavljevic M. (1999) *Magnetic Stimulation of the nervous system. In 'Modern Techniques in Neuroscience Research'.* Ed. U. Windhorst & H. Johansson. Springer-Verlag, Berlin Heidelberg. Chapter 33. Pp 869-892

Fleischmann A, Hirschmann S, Dolberg OT, Dannon PN, Grunhaus L. *Chronic treatment with repetitive transcranial magnetic stimulation inhibits seizure induction by electroconvulsive shock in rats.* Biol Psychiatry, 1999; 45 (6); 759-763

Gerwig M, Niehaus L, Kastrup O, Meyer BU. *Evaluation of cortical excitability by motor and phosphene thresholds in transcranial magnetic stimulation.* Klinische Neurophysiologie, 2002; 33 (4):196-199

Hausmann A, Weis C, Marksteiner J, Hinterhuber H, Humpel C. *Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus.* Molecular Brain Research, 2000; 76: 355-362

Keck ME, Engelmann M, Muller MB, Henniger MSH, Hermann B, Rupprecht R, Neumann ID, Toschi N, Landgraf R, Post A. *Repetitive transcranial magnetic stimulation induces active coping strategies and attenuates the neuroendocrine stress response in rats.* J of Psychiatric Research, 2000; 34 (4-5): 265-276

Kamida T, Fujiki M, Hori S, Isono M. *Conduction pathways of motor evoked potentials following transcranial magnetic stimulation: a rodent study using a 'figure-8' coil.* Muscle Nerve, 1998; 21 (6): 722-731

Kitagawa H, Moller AR. *Conduction pathways and generators of magnetic evoked spinal cord potentials: A study in monkeys.* Electroenceph Clin Neurophysiol, 1999; 93: 57-67

Kobayashi M, Ohira T, Ishihara M, Kawase T, Takase M. *Transcranial magnetic stimulation of the oculomotor and abducens nerves: Determining the site of excitation in the cat.* Journal of Clinical Neurophysiology, 1998; 15: 358-363

Levkovitz Y, Segal M. *Aging effects of transcranial magnetic modulation of hippocampal evoked potentials.* Neurobiology of aging, 2001; 22 (2): 255-263

Lisanby SH, Luber B, Perera T, Sackheim HA. *Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology.* International Journal of Neuropsychopharmacology, 2000; 3 (3): 259-273

Pascual-Leone A, Walsh V, Rothwell J. *Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry, and functional connectivity.* Current Opinion in Neurobiology, 2000; 10: 232-237

Shafik A. *Magnetic stimulation: a novel method for inducing evacuation of the neuropathic rectum and urinary bladder in a canine model.* Urology, 1999; 54(2): 368-372

Wang H, Wang W, Wetzel W, Scheich H. *Rapid-rate transcranial magnetic stimulation in auditory cortex induces LTP and LTD and impairs discrimination learning of frequency-modulated tones.* Electro Enceph and Clin Neurophysiol, 1999; 51: 361-367

Operating Room Monitoring

The Magstim BiStim can be twinned to form a set-up which is capable of very close interval (1ms+) trains of up to four pulses. Within the O.R. set-up it has proven possible to obtain clear, stable and large responses before, during and after spinal surgery. However, the uses of magnetic nerve stimulation around the operating room these days, are mainly confined to pre-and-post operative monitoring with direct electrical stimulation usually being the preferred choice to evoke motor potentials during surgery. The technique of using a dedicated nerve monitors to safeguard nerves at risk, often compliments the operation, particularly with appropriate surgical procedures such as facial nerve monitoring during acoustic neuroma, other brain surgery, thyroidectomies, spinal nerve roots etc.

Additionally magnetic stimulation's non-invasive and more comfortable characteristics give the advantage of allowing a pre-operative base line to be established and a post-operative assessments to be carried out. This enables meaningful comparisons to be made before, during and after surgery.

Aglio LS, Romero R, Desai S, Ramirez M, Gonzalez AA, Gugino LD. *The use of transcranial magnetic stimulation for monitoring descending spinal cord motor function.* Clinical Electroencephalography, 2002;33 (1):30-41

Krombach GA, Rohde V, Gilsbach JM. *Repetitive transcranial magnetic stimulation of the motor cortex: intraoperative monitoring.* Electroencephalography and Clin Neurophysiol,1998;106 (1001):24 S13-OP2

Pain

Magnetic stimulation is helping current researchers in the understanding and control of pain. As yet, the mechanisms by which magnetic stimulation may relieve pain are not clearly understood but it is known that both low and high intensity stimuli have proved superior to placebo in double blind trials.. Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex can induce a transient relief of chronic pain and may be a useful selection technique for predicting a favourable response to pain control from electrode implantation. Research into migraine has shown magnetic stimulation to be a very useful tool to look at the underlying pathophysiological conditions, but appears to be quite a long way from evolving a pain therapy.

Several studies have shown the relief of pain from peripheral applications of magnetic stimulation including localised musculoskeletal pain, and pain resulting from pudendal neuralgia and sciatica. Direct application of peripheral magnetic stimulation either over the painful area (muscular pain) or to a more remote innervating region such as the sacral region (S2-S3 interspace) for pudendal/sciatic nerve brought instant relief in many cases, with the duration of the relief reported as being from hours to weeks! Interestingly, a study by Nielsen showed the relief of pain in MS sufferers from muscle cramps through reduction of the underlying spasticity. While further research aimed at producing effective protocols is being undertaken, some physicians are already using magnetic stimulation as part of the therapy offered in their clinics.

Amassian VE, Vergara MS, Somasundaram M, Maccabee PJ, Cracco RQ. *Transcranial magnetic stimulation of human parietal lobe relieves induced pain through endorphin release.* Abstract from the Second World Congress for Electricity and Magnetism in Biology and Medicine, 8-13 June 1997

Aurora SK, Welch KMA, Al Sayed F. *The threshold for phosphenes is lower in migraine.* Cephalalgia, 2003; 23 (4): 258-263

Battelli L, Black KR, Wray SH. *Transcranial magnetic stimulation of visual area V5 in migraine.* Neurology, 2002; 58 (7): 1066-1069

Canavero S, Bonicalzi V, Dotta A, Vighetti S, Asteggiano G. *Low-rate repetitive TMS allays central pain.* Neurological Research, 2003; 25 (2): 151-152

Drouot X, Mnard I, Morales R, Lefaucheur JP. *Modulation of cortical excitability by rTMS in patients with chronic pain.* Electroenceph. Clin Neurophysiol,1999;110(1):PS-16.14

Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP. *The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone.* Brain, 2002;125(7)1660-1664

Migita K, Tohru U, Arita K, Monden S. *Transcranial Magnetic Coil Stimulation of Motor Cortex in Patients with Central Pain.* Neurosurgery,1995;36:1-4

Mulleners WM, Chronicle EP, Palmer JE, Koehler PJ, Vredeveld JW. *Visual cortex excitability in migraine with and without aura.* Headache, 2001; 41 (6): 565-572

Nielson JF. *Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study.* Multiple Sclerosis,1996;2:227-232

Pujol J, Pascual-Leone, et al. *The effect of repetitive magnetic stimulation on localised pain in skeletal muscles.* Neuro Report, 1998; 9:1745-1748

Rollnik JD, Wustefeld S, Dauper J, Karst M, Fink M, Kossev A, Dengler R. *Repetitive transcranial magnetic stimulation for the treatment of chronic pain - A pilot study.* European Neurology, 2002; 48 (1): 6-10

Sato T, Nagai H. *Sacral magnetic stimulation for pain relief from pudendal neuralgia and sciatica.* Diseases of the Colon & Rectum, 2002; 45 (2): 280-282

Peripheral Nerves

The stimulation of many peripheral nerves by magnetic stimulation has an ease and patient comfort unmatched by traditional electrical stimulation. Both methods have their strengths and weaknesses and these need to be recognised in order to achieve reliable results. There are many uses for single pulse magnetic stimulation in the areas of diagnosis and monitoring, such as in monitoring muscle strength in pulmonary disease. Repetitive magnetic stimulation is particularly useful in therapy such as peripheral pain relief and in the relief of spasticity post stroke and during MS. Further examples are given in our section on 'Rehabilitation'.

Sites of peripheral nerve stimulation are not necessarily the same for a closely spaced bipolar electrode and a biphasic or monophasic magnetic stimulating coil and they do not necessarily stimulate at exactly the same point. Exceptions are with superficial nerves where small double coils are shown to excite the nerve at the same point as conventional bipolar electrical stimulators when the cathode of the coil is positioned accurately. As the current flow between the two coils is counterclockwise, the induced current is at its maximum midway between the anterior point of the overlap of the two coils and a line tangential to its anterior edges. This midway point of maximum current is the position of the cathode (Binkofski et al. Muscle & Nerve, 1999; 22: 751-757). Magnetically induced electric fields preferentially depolarise at a point where the current is concentrated by anatomical features such as a bend in the nerve or a bony foramen, for example. Consistency of technique is therefore a must if results are to be meaningful.

Where a maximal muscle response is needed, electrical stimulator power levels can be increased until this can be achieved (limited by necrosis of tissue, pain or even dislocation of structures like the patella). This is not always the case with single pulse magnetic stimulators as in some instances, maximum power levels may be insufficient to achieve maximal muscle response. However, a high powered dual magnetic stimulator which can superimpose pulses, such as a BiStim unit connected with two Magstim 2002 stimulators, when coupled with the appropriate coil, usually has sufficient power to obtain a supramaximal muscle response from stimulation of deep nerves such as the femoral nerve. Polkey et al. 1996, achieved supramaximality at a mean of 83% of stimulator output from a single Magstim Model 200, from 10 normal subjects and 10 patients with suspected muscle weakness. It must be born in mind, however, that magnetic fields are at maximum close to the coils surface and fall away with increasing distance from the surface of the coil. Thus some obese patients, those with anatomical abnormalities or those with very thick dressings over the site of stimulation, may present some problems in this area. If your coil does not achieve supramaximal stimulation ask how. Do not assume that it cannot be achieved!

Benecke R. *Magnetic stimulation in the assessment of peripheral nerve disorders.* BailliPre's Clinical Neurology, 1996; 5:115-128

Binkofski F, Classen J, Benecke R. *Stimulation of peripheral nerves using a novel magnetic coil.* Muscle and Nerve, 1999; 22: 751-757

Harries ML, Moxham J. *Measuring respiratory strength using magnetic stimulation.* British Journal of Intensive Care, 1998; 8:21-28

Harris ML, Luo YM, Watson AC, Rafferty GF, Polkey MI, Green M, Moxham J. *Adductor pollicis twitch tension assessed by magnetic stimulation of the ulnar nerve.* Am J Respir Crit Care Med, 2000; 162: 240-245

Nielson JF. *Treatment of spasticity with repetitive magnetic stimulation; a double-blind placebo-controlled study.* Multiple Sclerosis, 1996; 2:227-232

Okabe S, Ugawa Y, Hanajima R, Shiio Y, Iwata N, Kanazawa I. *A new magnetic coil for stimulating the peripheral nerve.* Presented at the 42nd annual meeting of the Japanese Neurological Society. Tokyo, 2001

Pujol J, Pascual-Leone A, et. al. *The effect of repetitive magnetic stimulation on localised*

musculoskeletal pain. NeuroReport,1998; 9:1745-1748

Struppler A, Jakob C, Muller-Barna P, Schmid M, Lorenzen H-W, Paulig M, Prosiegal M. *New method for early rehabilitation in extreme palsies of central origin by magnetic stimulation.* Z. EEG-EMG 27(1996) 151-157. (German with English Abstract)

Terao Y, Ugawa Y. *Basic mechanisms of TMS.* Journal of Clinical Neurophysiology, 2002; 19 (4): 322-343

Plasticity

The ability of the brain to change or adapt to demands placed upon it plays a vital role in the adaptation of species to their environment. Since its inception, transcranial magnetic stimulation has played a very important role in the understanding of brain function and its reaction and modifications of cortical properties such as connectivity, neuronal modifications and representational patterns. The importance of these findings for the development of effective strategies to enhance plasticity when it is beneficial and to reduce its effects when it is not, is fundamental.

The following papers describe plasticity from many points of view: brain reorganisation following traumas such as stroke; central nervous system changes following intercostal nerve transfer; observations of cortical brain map changes following acquisition of new mental or physical skills etc.

Boniface SJ. *Plasticity after acute ischaemic stroke studied by transcranial magnetic stimulation.* Journal of Neurology Neurosurgery and Psychiatry, 2001; 71 (6) 713-715

Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stell R, Mastaglia FL. *The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection.* Brain, 1998; 121: 977-988

Carr LJ, Harrison LM, Evans AL, Stephens JA. *Patterns of central motor reorganization in hemiplegic cerebral palsy.* Brain 1993;116:1223-1247

Cohen LG, Ziemann U, Chen R, Classen J, Hallett M, Gerloff C, Butefisch C. *Studies of neuroplasticity with transcranial magnetic stimulation.* Journal of Clinical Neurophysiology, 1998; 15: 305-324

Corthout E, Uttl B, Walsh V, Hallett M, Cowey A. *Plasticity revealed by transcranial magnetic stimulation of early visual cortex.* NeuroReport, 2000; 11: 1565-1569

Duffau H, Denvil D, Capelle L. *Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy.* Journal of Neurology Neurosurgery and Psychiatry, 2002;72 (4): 511-516

Hallett M. *Functional reorganization after lesions of the human brain: studies with transcranial magnetic stimulation.* Revue Neurologique, 2001; 157 (8-9): 822-826

Hamdy S, Aziz Q, Rothwell J, Singh KD, Barlow J, Hughes D, Tallis R, Thompson DG. *The cortical topography of human swallowing musculature in health and disease.* Nature Medicine, 1996;11:1217-1224

Hamilton RH, Pascual-Leone A. *Cortical plasticity associated with Braille learning.* Trends in Cognitive Sciences, 1998; 2 (5): 168-174

Liepert J, Weiller C. *Mapping plastic brain changes after acute lesions.* Current Opinion in Neurology, 1999; 12 (6): 709-713

Malessy MJA, van der Kamp W, Thomeer RTWM, vanDijk JG. *Cortical excitability of the biceps muscle after intercostal-to-musculotaneous nerve transfer.* Journal of Neurosurgery, 1998, 89(4): 568-574

Pascual-LeonP A, Cammarota A, Wasserman EM, Brasil-Neto JP, Cohen LG, Hallett M. *Modulation of Motor Cortical Outputs to the Reading Hand of Braille Readers.* Annuls of Neurology, 1993;34:33-37

Roricht S, Machetanz J, Irlbacher K, Niehaus L, Biemer E, Meyer BU. *Reorganization of human motor cortex after hand replantation.* Annals of Neurology, 2001; 50 (2): 240-249

Rossi F, Triggs WJ, Eisenschenk S. *Topographic differences in task-dependent facilitation of magnetic motor-evoked potentials.* Neurology, 1999; 52:537-540

Rushworth M. *Stimulating plastic change.* Trends in Cognitive Sciences, 1998; 2 (11): 427

Schieber MH. *Rethinking the motor cortex.* Neurology, 1999; 52: 445-446

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. *Induction of plasticity in the human motor cortex by paired associative stimulation.* Brain, 2000; 123 (3): 572-584

Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernadi G. *Mapping of motor cortical reorganisation after stroke: A*

brain stimulation study with focal magnetic pulses. Stroke, 1997; 289:110-117.

Walsh V, Ashbridge E, Cowey A. *Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation.* Neuropsychologia, 1998; 36: 45-49

Ziemann U, Muellbacher W, Hallett M, Cohen LG. *Modulation of practice-dependent plasticity in human motor cortex.* Brain, 2001; 124 (6): 1171-1181

Psychiatry

Clinical research has revealed a number of uses for magnetic nerve stimulation from the use of single or double pulse systems to determine hyperexcitability or hypoexcitability of various cortical areas of the brain, to repetitive transcranial magnetic stimulation (rTMS) for therapeutic applications.

Among the potential therapeutic uses for repetitive transcranial magnetic stimulation are the treatment of psychiatric disorders such as depression, mania, obsessive compulsive disorder, schizophrenia, post traumatic stress disorder and Tourette syndrome.

Depression

Modest benefit in the treatment of depression was first demonstrated in 1995 by George et al. [NeuroReport, 1995, 6: 1853-1856] where sub-motor threshold magnetic stimuli were delivered cortically. The magnetic stimulation method is radically different from electroconvulsive therapy (ECT), in that the patients are alert and do not need to be anaesthetised. Follow up studies have shown a lack of adverse cognitive effects (Speer et al.) when using 1Hz or 20Hz repetitive transcranial magnetic stimulation at 100% motor threshold over left prefrontal cortex in depression. Indeed, one study showed improved executive functioning, Trail Making Test-B, raising the active group's mean score from just slightly less than the normative mean to the cusp of average and high average ranges (Moser et al. *Improved executive functioning following repetitive transcranial magnetic stimulation*).

There have been a number of other studies (see reference lists section on psychiatry) with a notable one having been conducted by Pascual-Leone et al. [Lancet, 1996b, 348: 233-238] where patients receiving repetitive transcranial magnetic stimulation (rTMS) to the left dorsal lateral prefrontal cortex, showed a significant improvement when compared with patients stimulated in other cortical areas.

Currently there are two approaches with regards to the treatment of depression with rTMS:

(a) repetitive high frequency stimulation, and

(b) repetitive low frequency stimulation.

Being more recent technique, repetitive low frequency stimulation is less well studied but appears to have similar beneficial effects to high frequency stimulation. If the initial data can be confirmed, the significantly lower risk of inducing a seizure will prove an undoubted positive for low frequency over the high frequency method. However, there is a school of thought that thinks that some forms of depression are manifest by either hyper-excitement of the right prefrontal cortex or by hypo-excitement of the left pre-frontal cortex. If this proves to be the case, then the correct treatment protocol will become self-evident

The majority of rTMS work has been done using a 10Hz frequency. Other frequencies researched include 1Hz, 5Hz, 15Hz, and 20Hz. It is standard practise to normalise the power levels used, to the threshold of a motor response in a relaxed thenar muscle, usually the right abductor pollicis brevis (APBM). This is a rough indicator of stimulating power and is a reasonable starting point in the absence of other indicators. Motor threshold is established by either holding the patients hand and feeling the twitch, by observation of a twitch, or by applying surface electrodes to the thenar muscles and measuring a 50V deflection over a number of stimulations. The motor threshold will vary in the normal population and with age, depending on the thickness of the skull; the elderly have some reduction in the fluid surrounding the brain, so that it is effectively further away from the coil. However, the motor threshold is also elevated in patients suffering depression; this is indicated in fMRI scans which show reduced electrical activity in this group.

With the motor threshold (MT) established, rTMS is then applied to the left dorsolateral prefrontal cortex (DLPFC) at a point 5 cm anterior to the scalp position for optimum stimulation of the right APBM in the parasagittal plane. The power levels range from 80% to 130% of motor threshold.

A study by Padberg et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity, showed that patients in the trial exhibited a Hamilton Depression Rating Scale (HRSD) decrease by 30% after 100% MT rTMS and by 15% after 90% MT rTMS.

A study by Janicak et al. using a frequency of 10Hz at 110% of motor threshold showed a 55% HRSD decrease for the rTMS group vs. a 64% for an ECT group. *Repetitive transcranial magnetic stimulation versus Electroconvulsive therapy for major depression: preliminary results of a randomised trial.*

Safe Limit Example: 10Hz Protocol

According to a study by Wassermann et al. (*Risk and safety of repetitive transcranial magnetic stimulation; report and suggested guidelines from the International Workshop on the Safety of repetitive transcranial magnetic stimulation*, June 5-7, 1996) the safe limit at 10Hz, is as follows:

80% of motor threshold	Limit unknown
100% of motor threshold	5 seconds (50 stimuli)
120% of motor threshold	4.2 seconds (42 stimuli)
130% of motor threshold	2.9 seconds (29 stimuli)

In the same paper it was suggested that studies in normal volunteers should be conducted with a 25% safety margin.

Safety Papers which are Essential Reading:

Wassermann EM, (1998). *Risk and safety of repetitive transcranial stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation*, June 5-7, 1996; Electroencephalogr Clin Neurophysiol, 1998, 108:1-16

Yvonne Turnier Shea, Marzena Ryback, Phil Reid, Saxby Pridmore. *Update on psychotropic medication used concurrently with transcranial magnetic stimulation.* German J Psychiatry, 1999; 2: 46-59

Magnetic Seizure Therapy (MST) is being researched as a possible alternative to ETC. Trials to date have suggested that there is a speedier postictal recovery of orientation and a lack of significant side effects when compared with ETC. However, clinical efficacy in the reduction of depression has not been fully established and further trials are currently underway.

Studies using rTMS have revealed cortical inhibition deficits in neuropsychiatric illnesses such as obsessive-compulsive disorder, schizophrenia and Tourette's disorder. Apart from auditory hallucinations however, therapeutic applications for rTMS in these areas have not been demonstrated.

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Chen R. *Transcranial magnetic stimulation: A new investigational and treatment tool in psychiatry.* Journal of Neuropsychiatry and Clinical Neurosciences, 2002, 14, (4), 406-415

Fitzgerald PB, Brown TL, Daskalakis ZJ. *The application of transcranial magnetic stimulation in psychiatry and neurosciences research.* Acta Psychiatrica Scandinavica, 2002;105(5):324-340

Greenberg BD, Ziemann U, Cora-Locatelli G. *Altered cortical excitability in obsessive-compulsive disorder.* Neurology, 2000; 54: 142-147

Janicak PG, Krasuski J, Beetle D, Ayd FJ. *Transcranial magnetic stimulation for psychiatric disorders.* Psychiatric Times, 1999; 16 (2): 1-10

Lisanby SH. *Update of magnetic seizure therapy: a novel form of convulsive therapy.* The Journal of ECT, 2002; 18(4): 182-188

Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. *Improved executive functioning following repetitive transcranial magnetic stimulation.* Neurology, 2002; 58(8):1288-1290

Mnchau A, Bloem BR, Thilo KV, Trimble MR, Rothwell JC, Robertson MM. *Repetitive transcranial magnetic stimulation in Tourette syndrome.* Neurology, 2002; 59: 1789-1791

Padberg F, Zwanzger P, et al. *Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity.* Neuropsychopharmacology, 2002; 27 (4):638-645

Speer AM, Repella JD, Figueras S, Demian NK, Kimbrell TA, Wasserman EM, Post RM. *Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression.* Journal of ECT, 2001, 17, (4): 259-263

The Avery-George Database of rTMS studies of depression is available on their Internet site at: http://www.ists.inibe.ch/ists/TMSAvery.htm This

site lists protocols from past and present researchers together with a log of their results.

Mania

Few studies of mania have been carried out using Transcranial Magnetic Stimulation although there are many studies showing the efficacy of Electroconvulsive therapy (ECT). TMS studies utilising small groups of patients with stimulation of the right pre-frontal cortex suggest that it has therapeutic effects. In initial trials, significant benefits to patients occurred within 14 days, about the same period of time in which ECT becomes effective.

Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. *Transcranial magnetic stimulation in mania: A controlled study.* American Journal of Psychiatry, 1998;155 (11):1608-1610

Kaptsan A, Yarowslavsky Y, Applebaum J, Belmaker RH, Grisaru N. *Right prefrontal versus sham treatment of mania: a controlled study.* Bipolar. Disord. 2003; 5(1): 36-39

Shaldivin A, Kaptsan A, Belmaker RH, Einat H, Grisaru N. *Transcranial magnetic stimulation in an amphetamine hyperactivity model of mania.* Bipolar Disorders, 2001; 3 (1): 30-34

Schizophrenia

While very few studies have been carried out into the efficacy of rTMS as a treatment tool for schizophrenia, indications of its value as a possible treatment of is encouraging. Klein et al. did not find a significant response to 1Hz rTMS to the right prefrontal cortex of patients with schizophrenia or schizoaffective disorder. In contrast, Rollnick et al. demonstrated a significant reduction in symptoms as rated by the Brief Psychiatric Rating Scale, after a two week double-blind cross over study using high frequency rTMS to the left dorsolateral prefrontal cortex. Hoffman et al. conducted a recent trial with twenty-four patients with schizophrenia or schizoaffective disorder and medication- resistant. Patients were randomly selected to receive 1Hz rTMS or sham stimulation for 9 days at 90% of motor threshold. Auditory hallucinations were robustly improved with rTMS relative to sham stimulation. Duration of effects ranged widely, with 52% patients maintaining improvement for at least 15 weeks.

Hoffman et al. *Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations.* Archives of General Psychiatry, 2003;60(1): 49-56

Klein E, Kreinen I, Christyakov A, Puyerovsky M, Koren D, Christyakov A, Feinsod M. *Right frontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham controlled pilot study.* Biol Psychiatry, 2000; 46 (10): 1451-4

Rolnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengler R, Emrich HM, Schneider U. *High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients.* NeuroReport, 2000; 11 4013-4015

Also see the Safety section and the References.

Psychology

Human and animal brain function and behaviour have long been the subject for speculation, study and experiment. Transcranial magnetic stimulation (TMS) provides a vital tool which adds a further dimension to psychological studies. Its world-wide use in the investigation of learning, memory, speech, hearing, visual perception and in functional connectivity between different brain areas is supported by both the number of research departments using this technique and by the wealth of their published papers.

Various studies have shown that a major function of TMS lies in its ability to non-invasively create a temporary lesion, with a high degree of spatial and temporal resolution. The 'virtual' lesions created by TMS differ from lesions seen in neuropsychological patients in two important ways, by being both transient and reversible (Stewart et al.). It can either prevent the arrival of a critical signal or prevent the output of a processing stage (Walsh et al.). Its uses include visual detection, discrimination, attention and plasticity. Phosphenes can be evoked, even in non-sighted subjects. Disruption of ongoing speech processes have been observed following the application of repetitive transcranial magnetic stimulation (rTMS), over frontal or parietal areas of the dominant hemisphere. Applying rTMS to Wernicke's area leads to a brief facilitation of picture naming by shortening linguistic processing time (Mottaghy et al.).

Other areas of interest include the ability of TMS to measure cortical inhibition and facilitation, neural plasticity, and when coupled to an electroencephalogram (EEG), to measure cortico-cortical connectivity. TMS has been shown to have therapeutic properties when used in the

study of some psychiatric problems such as depression, and in the treatment auditory hallucinations in schizophrenia (Daskalakis et al).

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Chen R.. Transcranial magnetic stimulation: A new investigational and treatment tool in psychiatry. Journal of Neuropsychiatry and Clinical Neurosciences, 2002; 14 (4): 406-415

Floeter MK, Rothwell JC. Releasing the brakes before pressing the gas pedal. Neurology, 1999;

53: 664-665

Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K, Krystal JH.

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Jahanshahi M, Profice P, Brown RG, Ridding MC, Dirnberger G, Rothwell JC. The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. Brain, 1998;121 (8):1533-1544

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Rehabilitation

Muscle injury

Electrical stimulation has long been used as an aid to promote muscle recovery from trauma, and to help to train muscle as a way of improving strength. Unfortunately the benefits are limited by pain and patients will not continue a course of therapy if it hurts! Magnetic stimulation has proved capable of both training muscle and of improving its fatigue resistance. With the introduction of repetitive stimulation it is poised to take over the more mundane tasks of the physiotherapists, and in some instances may become a guide as to when physiotherapy will be most beneficial.

Relief of Spasticity

Two groups have published papers showing relief of spasticity with post stroke and MS patients. They are convinced that rapid rate stimulation applied at an early stage can prevent spasticity occurring.

Simulation of a Cough

Techniques using both single twitch and repetitive magnetic stimulation have been developed to aid spinally injured patients.

Urology

Assisting micturition and relieving idiopathic detrusor instability are some of the potential benefits evolving from recent research.

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Spinal Injuries

Cervical Spondylosis

Magnetic stimulation is also used in the early diagnosis and assessment of spinal disorders such as Cervical Spondylosis. The testing procedure is simple, takes less than 45 minutes to carry out in the majority of cases, and is virtually painless.

The tests are based on the fact that the muscles in the shoulders and arms are fed from different cervical nerve roots and that the anatomical connections are well understood. By looking at the responses from carefully chosen muscle groups following cortical and peripheral stimulation, the progress of the impulse can be monitored through the brain, specific nerve roots and nerve trunks. The muscles commonly used are the Biceps, typically fed by C5, C6, and C7 nerve roots, and First Dorsal Interosseous (FDI), typically fed by C8 and T1 nerve roots (see Figure 16). This choice allows the differentiation between upper and lower cervical disorders.

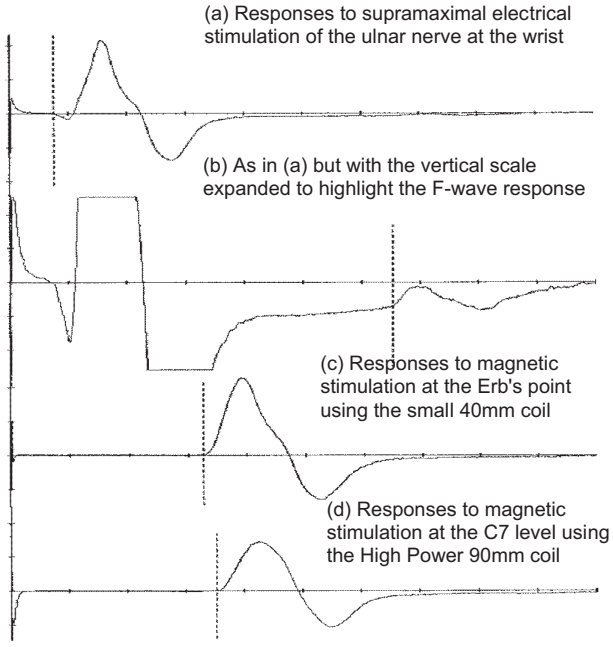

Figure 39: The example waveforms shown here have all been recorded over the left first dorsal interosseous (FDI). Since the FDI muscle is fed by the ulnar nerve supplied by the C8 and T1 nerve roots, the above measurements allow for the assessment of lower cervical roots. Vertical Scale: 5mV/Div for responses (a), (c) and (d) and 0.5mV/Div for response (b). Horizontal Scale: 5ms/Div

The stimulating coil is used cortically and responses are obtained from the left and right Biceps and FDI. The coil is then positioned over the cervical nerve roots and at the Erbs point and responses are once again recorded from the left and right muscles. In the case of the FDI muscles conventional F-wave recordings can also be used to differentiate between central and spinal nerve root lesions. Example response waveforms are shown in Figure 39.

The latency, amplitude and waveform measurements are sensitive indicators of location and severity of cervical spine disorders. In addition, comparison of the responses from left and right hand sides allows the determination of the laterality of the abnormality. The test is used to indicate, quantify and monitor the progress of the spinal disorder, confirm radiological and clinical findings, and also to indicate the level of involvement of motor pathways in patients with soft tissue injury.

Sports Medicine

Stroke

The first extensive study of central motor conduction time (CMCT) post stroke was conducted under the auspices of Professor Simon Miller at Newcastle University Medical School in the early 1990's. The study was performed on 118 patients with first ever stroke to determine the changes to CMCT in upper limb muscles. In the ten years since the results of the Newcastle study was published in 1993 many supportive stroke studies have been published to date. While the majority of these papers are looking at cortical changes in the brain post stroke, physiological effects and ways to monitor these changes, many have a leaning to prognostic and therapeutic aspects.

Basically, the technique of magnetic stimulation appears useful for the prognosis and monitoring of stroke affecting the central motor nervous system. When applied soon after the onset of stroke - within 7 days - it provides important early data regarding the prospects of recovery, especially movement. It is a quick test to conduct and its non-invasive nature allows for repeated use to monitor progress without patient discomfort.

Accurate diagnosis of stroke is currently achieved through clinical examination and scanning techniques. It is, however, difficult to determine the prospects for recovery. Such information is important to determine patient need, arrange physiotherapy where appropriate, and give relatives a more accurate indicator of recovery. Motor evoked responses present on the paretic side predict good recovery and an absence of any response indicates poor recovery. The test is simple and quick to carry out and when needed, other parameters such as response amplitude, stimulation thresholds and conduction latency can also be determined.

Interpretation of Results: A normal response predicts good and complete recovery whereas absence of a response indicates poor recovery. In some 5-10% of patients some degree of recovery is possible without an initial response, but complete recovery remains unlikely. Abnormal thresholds, small response amplitudes or a long CMCT all indicate motor nerve involvement. The prognosis is variable to good depending on the number of parameters which are abnormal. Where magnetic stimulation is carried out in the first few days, the results form the basis of a very early prognostic indicator of motor recovery.

Thoracic Medicine

Phrenic Nerve Stimulation

The Magstim is used for bilateral or unilateral phrenic nerve stimulation. Its advantages over electrical stimulation are ease of positioning, repeatability and much improved patient tolerance. It is used reliably to assess the function of respiratory muscles by measuring the diaphragmatic response and strength. The ease of application and patient comfort makes it possible to also carry out longitudinal monitoring studies. Magnetic stimulation can be used to obtain responses even when the phrenic nerve cannot be located using conventional electrical stimulation.

Twitch Pdi measurement may be used to confirm or refute the diagnosis of bilateral or unilateral diaphragm weakness. In patients with neuromuscular disease Twitch Pdi may permit accurate clinical assessment of disease progress. Ongoing developments include the adaptation of magnetic stimulation for use with neonates or children. Additionally, by measuring pressure changes in the mouth (Twitch Pmo) it is now possible to obtain a non-volitional measure of diaphragm strength.

Urology

Recent advances in the diagnosis and monitoring of urogenital tract dysfunction have become of interest to the Urologist, Neuro-Urologist and Urosurgeon alike. The contribution of the somatic fibres to the innervation of the lower genitourinary tract is marginal compared to that of the autonomic nerves. Magnetic stimulation allows the investigation of central motor pathways and autonomic nerve function alongside the more traditional techniques which look at somatic pathways only.

Pelvic floor motor evoked potentials (MEPs), in response to either cortical or peripheral stimulation, can be recorded on standard EMG or evoked potential equipment. Responses can be picked up by concentric needle electrodes from the muscles concerned (e.g. anal or periurethral sphincter, bulbocavernosus muscles, or detrusor muscle), or by sphincter plugs containing silver plated electrodes.

Stimulation of the motor cortex gives an overall response which includes conduction along both the central and peripheral portions of the motor pathways. As an example stimulation of lumbosacral nerves and roots, as shown in Figure 40, is also possible.

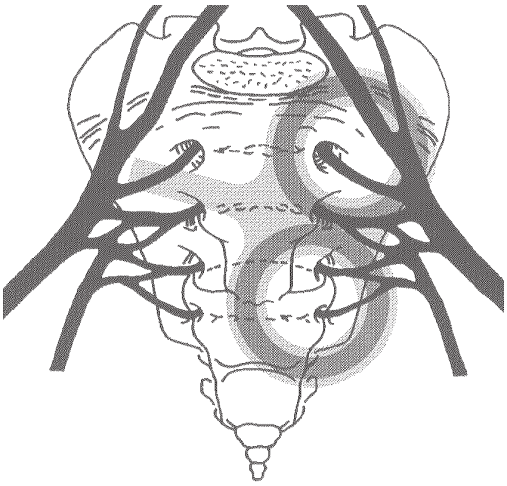

Figure 40: The 200^2 can be used for the stimulation of lumbosacral nerve roots. Here the Double 70mm coil is used to provide improved accuracy of stimulation

By subtracting the response latency to peripheral stimulation from the response latency to cortical stimulation, the central motor conduction and spinal root conduction time is obtained. The

results can then be compared to tables of normal responses for interpretation. Both congenital and acquired disorders such as menigomyeloceles, multiple sclerosis, Parkinsons disease, pelvic floor disorders including lesions of the sacral cord, corda equina, the motor branch of the pudendal nerve, and fractures of the pelvic bones, can be evaluated by this method. Recent research is revealing exciting prospects for non invasive control over bladder emptying and bladder training. (see section on Therapy - Urology)

Additionally magnetic stimulation of the lumbar spine can be used to record sensory evoked potentials from the sensory cortex. The main advantage is that of patient comfort where conventional electrical stimulation may be unbearable [Tsuji S, et al. Cortical Somatosensory Potentials Evoked by Magnetic Stimulation of Thoracic and Lumbar Roots. Neurology, 1993, 43: 391-396]. New clinical papers are emerging which point the way to advanced applications for repetitive stimulation both in diagnosis and therapy.

Safety Precautions & Issues

The presence of pacemakers and other electronic implants must be considered as a contraindication in case of interference due to the induced electric fields and currents resulting from the magnetic pulse. Although the stimulating coil does not have much effect on small metallic objects, such as stainless steel aneurysm clips placed a few inches away, it could exert a more significant physical force on larger metal objects within 20cm of the coil. Much depends on the size of the object, its conductivity and whether or not it is ferromagnetic. Data on magnetic materials such as credit cards and computer floppy discs can be accidentally erased and cathode ray tubes, especially those with a colour mask, could be affected if they were brought within some 50cm of the stimulating coil.

Studies with very powerful magnetic stimulators with energies of 10kJ or more, giving an order of magnitude increase in stimulating power over conventional stimulators, have shown that it is possible to induce an ectopic beat in a dogs heart [Bourland, et al. Med Biol Eng & Comput, 1990, 28: 196-198]. It is not possible, however, to directly affect the human heart with any of today's commercial magnetic stimulator units due to their limited discharge energy, the distance from the coil to the heart and also the relatively fast pulse rise time of the magnetic field waveform. Clinical magnetic defibrillators, however, remains a possibility for the future.

Kindling is a phenomenon whereby a permanent epileptic focus is induced by very many repetitive stimuli given to the brain using implanted electrodes. Goddard et al. [Goddard et al. Exp Neurol, 1969, 25: 295-330] were unable to induce kindling in animals at frequencies of less than 10Hz, irrespective of the number of stimuli given. Using magnetic stimulators, with a maximum discharge repetition rate of less than 1Hz, no risk of kindling should exist. In addition, the number of stimuli given to any one subject is very low compared to the minimum required to cause kindling in animals. The risk of kindling in the case of fast repetitive magnetic stimuli (10Hz) remains unknown.

In Table 2 the calculated figures of magnetic and electric field strengths, induced current, charge density, and deposited tissue energy are provided for the Magstim 200 together with the original Sheffield Magstim. In the calculation of these parameters, used for considering the physiological effects of the magnetic stimulator on humans, it has been assumed that the brain does not lie closer than 5mm to the coil surface. Other than in the case of exposed brain this should normally be the case. A uniform conductivity value of 0.35S/m, that of grey matter in humans [Geddes & Baker, Med Bio Eng, 1967, 5: 271-293], has been used in the calculation of induced current, charge density per phase and energy deposited per pulse. It should be noted that these calculations are carried out to estimate the maximum exposure levels and are likely to be over-estimates.

There is little evidence to suggest that magnetic fields of the order of 2T can have any harmful effect. The current UK guidelines for whole body exposure to static magnetic fields during magnetic resonance imaging is 2.5T [NRPB, Radiograph 1984, 50: 220]. In addition it should be remembered that, in most cases, the output from a magnetic stimulator lasts only 1ms and there is no obvious reason why purely magnetic effects from such a pulse should be greater than from a static field.

The figures in Table question show that the maximum electric field and induced current density are 540V/m and 19mA/cm2 respectively. As expected these levels of exposure are similar to conventional electrical stimulation using surface or needle electrodes which have proven quite safe. In

addition the induced stimulus from the magnetic stimulator is inherently charge balanced, eliminating the possibility of electrolytic cell damage in cases of prolonged stimulation. The figure of charge density per phase of 1.1mC/cm2/phase is well below the minimum figure of 40mC/cm2/phase at which evidence of neural damage has been found when stimulating for long periods at 50Hz [Agnew et al. Neurosurg, 1987, 20: 143-147]. In addition the total charge delivered is less than 0.1% of that used for ETC. The maximum calculated figure of 5.3mJ/cm3 for the energy density per pulse dissipated in tissue is extremely small, giving a temperature rise of only 10-6C in the tissue. At a repetition rate of 1Hz, the total power dissipation of less than 1mW for the whole brain is more than four orders of magnitude lower than the adult brain base metabolic rate.

It has been suggested by Counter et al. [Neurology, 1990, 40: 1159-1162] that the discharge click noise produced by a 5cm stimulating coil causes hearing loss in albino and chinchilla rabbits with the coil placed over the external auditory meatus. The sound output from the coil was measured to be as much as 157dB peak SPL. Barker and Stevens [Physiology Soc, London, 1991, 19: 14P] measured sound output from the standard commercial coil (Type 9784 in Table 1) supplied together with the Magstim 200 and found it to be a maximum of 124dB(A) on the coil surface falling to 117dB(A) 50mm away from the coil surface. These values are within that required by the UK Noise at Work Regulations (1989) as long as the number of discharges at the maximum power level does not exceed 4000 stimuli per day - clearly an unlikely event. It should be noted that the discharge click noise depends on the coil size (small coils are louder than larger versions), power level and most importantly the manufacturing method.

Low Frequency Stimulation

Since 1985 many tens of thousand of subjects have been examined using low repetition rate (<1Hz) magnetic stimulators to assess motor function of the peripheral and central nervous system. There is now a considerable volume of data supporting the safety of magnetic stimulation. There have been no ill effects reported with magnetic stimulation of the peripheral nervous system and in the case of cortical stimulation the incidence of side effects has been extremely low and well within that expected by available statistics for various patient groups [Kandler R, Lancet, 1990, 335, 1: 469-70]. An area of concern has been the triggering of epileptiform activity in individuals at a high risk to epilepsy [Homberg & Netz, 1989, 2: 113]. Nevertheless one of the areas where magnetic stimulators have been successfully used has been in the study of epilepsy and the determination of the site of the epileptic focus [Hufnagel et al. Ann Neurol, 1990, 27: 49-60]. Overall magnetic stimulation has proved to be a very safe and effective clinical tool.

High Frequency Stimulation Guidelines

Recommended Reading

Wassermann EM, (1998). *Risk and safety of repetitive transcranial stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation*, June 5-7, 1996; Electroencephalogr Clin Neurophysiol, 1998, 108:1-16

Yvonne Turnier Shea, Marzena Ryback, Phil Reid, Saxby Pridmore. *Update on psychotropic medication used concurrently with transcranial magnetic stimulation.* German J Psychiatry, 1999; 2: 46-59

The high level of interest now shown in TMS and rTMS has led to the formation of the International Society for Transcranial Stimulation, ISTS, which will become a representative and supportive body, co-ordinating developments at both the scientific and regulatory level. The International Federation of Clinical Neurophysiology has appointed a Special Commission to make recommendations for the world-wide use of TMS and the American Academy of Neurology has appointed a Commission to evaluate the clinical usefulness of TMS and to develop a position statement for the AAN on the issue of recommendations for the technology.

Related Web Sites

www.ists.unibe.ch

www.ists.inibe.ch/ists/TMSAvery.htm
www.musc.edu/tmsmirror/TMSresrc.html

www.psycom.net/depression.central.transcranial. html

http://info.utas.edu.au/docs/healthsci/inro/layintro .html

http://info.utas.edu.au/docs/healthsci/articles.html

www.psych.helsinki.fi128.214.75.169/magstim.h tml

www.magstim.com

Further Information: This guide, based on the original 'Guide to Magnetic Stimulation' by Dr. Reza Jalinous, has been produced in response to numerous requests for an updated version. With the huge increase in subjects undergoing serious research in recent years, with some applications already becoming clinical practise in many countries, the numbers of published papers has gone from a trickle to a torrent. Therefore, any 'Guide to Magnetic Nerve Stimulation' can be nothing more than a 'Guide'. For modifications and corrections please contact:

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