24.3.4 Investigation of central motor pathways Mag

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24.3.4 Investigation of central motor pathways: Magnetic brain stimulation 5817 represent a major revolution in the management of patients with aneurysmal SAH and other complex neurovascular conditions. FURTHER READING Atlas S (2008). Magnetic resonance imaging of the brain and spine, 4th edition. Lippincott Williams & Wilkins, Philadelphia, PA. Barkovich AJ, Raybaud C. (2011) Paediatric Neuroimaging, 5th edition. Lippincott Williams & Wilkins, Philadelphia, PA. Osborn AG (2012). Osborn's brain: imaging, pathology and anatomy. Amirsys, Salt Lake City, UT. 24.3.4 Investigation of central
motor pathways: Magnetic brain stimulation K.R. Mills ESSENTIALS The ability to stimulate percutaneously the central nervous system of conscious humans without causing pain has opened up new areas for neurophysiological investigation in the early diagnosis of neurological disease, and has furthered the understanding of normal and abnormal motor control. Magnetic stimulators are now available that can excite both upper and lower limb areas of the motor cortex, as well as cranial nerves, motor roots, and deeply sited peripheral nerves. Clinical applications—these include: (1) measurement of central motor conduction time—this is prolonged in some cases of mul- tiple sclerosis, the threshold is usually raised in motor neuron dis- ease, and the technique may be useful in cerebellar ataxia, including Friedrich's ataxia; (2) assessment of completeness of spinal cord
injury; and possibly (3) evaluation of neurodevelopmental delay in children with neurodegenerative and other related diseases. The technique can be used serially to monitor progress of disease or after neurological injury or to examine the effects of drugs, and it can be used safely in neonates and children. Magnetic stimulators The magnetic stimulator is an essentially simple device: a brief

pulse of electric current is passed through a coil which then generates an intense magnetic field permeating unattenuated into the sur- rounding media. Any electrical conductor, such as the brain, in the vicinity of the coil will have currents induced within it; these induced currents are capable of exciting cerebral neurons. Coils are placed on the scalp and may be plane circular, figure of eight, or double cone in geometry, the last being especially effective in exciting leg areas of the motor cortex. Some magnetic stimulators produce a predom- inantly monophasic field pulse, others multiphasic pulses; with the former, the side of the coil next to the scalp determines which hemi- sphere is predominantly excited, whereas with the latter both hemi- spheres are about equally excited. Physiology If a single electrical anodal shock is applied to the exposed cortex of a monkey and recordings are made from the pyramidal tract, it is seen that, if stimulus intensity is sufficient, an initial wave pro- duced by direct activation of pyramidal tract neurons (the D wave) is followed by a variable number of other waves produced by indirect trans-synaptic activation (I waves) of the same pyramidal neurons. In humans a single weak magnetic stimulus to the scalp probably excites pyramidal tract cells trans-synaptically; stronger stimuli may excite the cells directly. The effect of a single stimulus is to cause a high frequency (500–1000 Hz) burst of impulses to descend in the fastest fibres of the pyramidal tract; the spinal motoneurons are en- gaged by these impulses and, if their excitability is high enough and there is sufficient temporal and spatial summation, the motoneurons fire, causing a muscle contraction. There is considerable conver- gence and divergence of pyramidal tract fibres within motoneuron pools: single spinal motoneurons receive many corticospinal inputs and, conversely, single pyramidal tract fibres branch to supply many spinal motoneurons. Intrinsic hand muscles are the most easily ex- cited by brain stimulation, but all voluntary muscles appear to be accessible via cortical stimulation. The amplitude of response of a muscle depends on the intensity of the stimulus, to a lesser extent on coil placement on the scalp, but most potently on the degree of voluntary preactivation of the muscle. Thus, the amplitude of response of an intrinsic hand muscle may be 20–30 times greater if the individual performs a gentle (5– 10% maximum) voluntary contraction of the muscle. This facilita- tion is probably due to both cortical and spinal cord mechanisms, voluntary action increasing the effectiveness of the stimulus at the cortex, at the same time as the excitability of spinal motoneurons is increased by other pathways. The latter mechanism predominates in intrinsic hand muscles. Clearly, many factors, including mental set, affect the size of muscle response to the stimulus, and it should be emphasized that this phenomenon of response variability contrasts with the identical and reproducible responses obtained from max- imal electrical peripheral nerve shocks; central motor conduction studies should not be regarded simply as an extension of nerve con- duction measurements. Single scalp shocks also bring into play inhibitory mechanisms: if an individual maintains a steady voluntary muscle contraction, the initial excitation caused by the stimulus is followed by a silent period, due to the inhibition of voluntary action. Experiments with paired cortical stimuli have established short interval intracortical inhibition where a subthreshold conditioning stimulus reduces the effects of a subsequent test stimulus if the interstimulus interval is 1–5 ms, and long interval intracortical inhibition, probably corres- ponding to the silent period (mentioned earlier) where the response

 to the second of a pair of equally intense stimuli is less if the interval between them in 50–150 ms. A triple stimulation technique in which stimuli to the cortex, wrist, and Erb’s point are carefully timed to produce collisions, can directly quantify the degree of corticospinal tract excitation. This has proved clinically useful in serially moni- toring amyotrophic lateral sclerosis. Safety of magnetic stimulation Several studies have looked at the

acute effects of magnetic stimuli on animals. It has been shown that magnetic stimuli have little de- tectable effect on the heart rate, arterial blood pressure, or cerebral blood flow in cats. Magnetic brain stimulation has no acute ef- fects on the human electroencephalogram or on the performance of simple cognitive tests. There have currently been no reports of adverse effects in healthy humans, but, clearly, workers in the field should remain vigilant, especially for long-term effects. It has been calculated that the total amount of power dissipated in the brain during magnetic stimulation is 1.8 μJ/cm3 per stimulus and, at the maximal rate of stimulation of 0.3 Hz, the average power dissipation is 53 μW, some five orders of magnitude below the basal metabolic rate of the brain. It was considered prudent for early users of magnetic stimulation to exclude patients who had a history of epilepsy from their studies. Since then, magnetic stimulation has actually been used to attempt to localize epileptic foci in patients with intractable seizures. Despite magnetic stimulation devices being used on many thousands of pa- tients, many of whom must have had a predilection for epilepsy, there have been only a few reports of a fit being related to single- pulse brain stimulation. Measurement of central motor conduction time The latency of muscle response has a central and a peripheral com- ponent and a delay due to synaptic transmission in the spinal cord. There is good evidence that, at least with limb muscle, the con- nection from the pyramidal tract to spinal motoneuron is mono- synaptic. The central component of conduction—central motor conduction time—can be estimated by subtracting from the cortex to muscle latency an estimate of the peripheral conduction time obtained either from F-wave measurement (see Chapter 24.3.2) or from responses evoked by root stimulation. In healthy individuals, the mean latency (± standard deviation) of responses in intrinsic hand muscle is 19.7 ± 1.2 ms and the central motor conduction time is 6.1 ± 0.9 ms. The amplitude of responses from brain stimu- lation is usually compared with that obtained from maximal per- ipheral nerve stimulation; again, there is great variability, but in healthy individuals the response from cortical stimuli is usually at least 15% of that from nerve stimulation. As many factors can influence these values, each laboratory should develop its own nor- mative database. Motor roots may be excited by both electrical and magnetic stimu- lators. The former method is preferable because it is not possible to obtain maximal responses in all healthy individuals with mag- netic coils, even with optimal coil geometry, coil orientation, and coil position. Both devices activate motor roots at or just outside the intervertebral foramina, and so peripheral conduction time es- timated by this method omits conduction in the small segment of motor root within the spinal canal, and central motor conduction time is slightly overestimated. The method must be used, however, if F waves are unobtainable. Compound responses from muscle may be recorded with sur- face electrodes, or single motor unit responses may be recorded with needle electrodes; the former method is used clinically, the latter is useful in research. Several parameters of the surface- recorded response are useful: the maximum amplitude, the onset latency with the muscle relaxed or contracted, the threshold for evoking a response and the input:output relation giving a measure of cortical excitability or inhibitability. Prolongation of central motor conduction time has been reported in many conditions and is not specific. Delay can be produced by a variety of pathological processes: demyelination of central fibres can lead to slowing of impulse propagation in the central motor pathway; desynchronization of descending impulses can lead to loss of temporal summation at the motoneuron and delay in its firing; and loss of corticospinal axons can lead to impairment of spatial summation at motoneurons and can again delay firing. Multiple sclerosis In multiple sclerosis, central motor conduction time is prolonged in about 70% of cases when there are clear clinical signs of a pyr- amidal lesion in a particular limb (Fig. 24.3.4.1). The delay in some cases is very considerable: central motor conduction time may be up to five times longer than in controls. It

is likely that, in these cases, demyelination of central fibres is the mechanism leading to delay. In other cases, delay is more modest, only a few milliseconds, Cortex Wrist 11.6 ms 11.8 ms 10 ms 5 mV 25.5 ms 19.2 ms 1 mV Right Left C7/T1 Fig. 24.3.4.1 Slowing of central motor conduction in multiple sclerosis. Compound muscle action potentials are recorded with surface electrodes over the left and right abductor digiti minimi muscles. Stimuli are given to the ulnar nerve at the wrist (left), the C7 to T1 motor roots (middle), and the motor cortex (right). Onset latencies are shown and the variability of responses from cortical stimulation can be seen. On the left, the central motor conduction time is 7.4 ms, but on the right is prolonged at 13.9 ms.

24.3.4 Investigation of central motor pathways: Magnetic brain stimulation 5819 and the mechanism is less certain. Abnormal central motor con- duction appears to correlate most closely with exaggerated reflexes and spasticity rather than with weakness or cerebellar signs in the limb. Abnormal central motor conduction time from leg areas of motor cortex also correlates with the finding of extensor plantar responses. Central motor conduction can, however, be abnormal even in the absence of clinical signs. In a large series, it was found that cen- tral conduction was abnormal in 20% of cases of multiple sclerosis with no motor signs in the particular limb. The technique can thus be used as a screening test for the disease, although it compares unfavourably with visual-evoked potentials, which have a higher rate of abnormality in the absence of clinical signs. This may merely reflect the greater accuracy with which the motor system can be examined clinically. Central motor studies may also be helpful in deciding on the importance of equivocal motor signs, such as mild impairment of fine finger movements. Motor neuron disease In motor neuron disease, the most common abnormality is a raised threshold for excitation of the motor cortex, although in early cases the threshold may be reduced. In some cases, responses cannot be obtained even with the strongest stimuli applied in optimal condi- tions. Central motor conduction time may be prolonged, but usu- ally only modestly, and responses are often reduced in amplitude in comparison with responses evoked by maximal nerve stimulation. The more muscles that are examined, the greater is the likelihood of detecting an abnormality. The test can be used to confirm an upper motor neuron component to weakness when lower motor neuron signs predominate or for detecting an upper motor neuron lesion in a limb without clinical signs. Cerebrovascular disease In stroke, responses in an affected limb may be normal, delayed, or absent, with abnormality grossly paralleling the clinical abnor- mality. Central motor conduction studies have been used to predict outcome of stroke; if performed within the first 48 h after the ictus, a poor outcome at six months is predicted by absent responses and a favourable outcome by normal responses. Whether the prediction is superior to that made purely on clinical grounds is uncertain, but at least the method is quantitative and can be used serially to follow recovery. Movement disorders Most studies have shown central motor conduction to be normal in Parkinson’s disease, multiple system atrophy, Wilson’s disease, Huntington’s disease (including at-risk relatives), dystonia, and progressive supranuclear palsy. In some cases of Wilson’s disease, central conduction delays have been found. In all these conditions, however, there may be subtle changes in motor cortex excitability detectable as a change in threshold or an abnormal inhibitory re- sponse to appropriately timed pairs of cortical stimuli. Degenerative neurological diseases Several rarer degenerative diseases have been investigated with the technique: Friedreich’s ataxia often shows delayed and dispersed re- sponses, as does early onset cerebellar ataxia with retained reflexes, the severity of the abnormalities reflecting disease duration. In late- onset cerebellar degeneration, on the other hand, the responses are normal in 62% of cases. In hereditary spastic paraparesis and tropical spastic paraparesis, responses from upper limb muscles are usually

normal, whereas those from the lower limbs are delayed or absent. Abnormalities of central motor conduction have also been described in some cases of hereditary motor and sensory neur- opathy types I and II, the abnormalities being found especially in those patients with additional upper motor neuron signs. Central motor conduction abnormalities have also been described in a family with hereditary motor and sensory neuropathy with pyram- idal signs (HMSN type V). Spinal cord lesions Magnetic brain stimulation has been used to assess the complete- ness of spinal cord injury. A variety of facilitating techniques must be used; the modulation of flexion reflexes by brain stimuli has been shown to be useful in establishing whether injury is complete; in 4 of 26 patients evidence of incomplete lesions was found in patients with clinically complete spinal cord injuries. In compressive myel- opathy, by recording from a variety of upper limb muscles, central motor conduction time can be used to localize more accurately the compressed cord segment. This can prove useful to the neurosur- geon when there are multiple levels of compression on imaging. Paediatric applications The central conduction time in a group of 457 normal individuals between the ages of 32 weeks and 55 years has been determined. It was found that central conduction time decreases rapidly over the first two years of life and then remains constant at the adult value. In contrast, peripheral conduction increases in proportion to arm length after the age of five years. It is suggested that this constant central delay could be useful during the acquisition of motor skills. Central motor conduction has been studied in a range of neuro- logical diseases in children. For example, in 13 of 20 children with an upper motor neuron syndrome of varied aetiology, the central conduction time was abnormal, but magnetic resonance imaging and/or computed tomography showed focal abnormalities in only seven. In cerebral palsy, responses are often absent. In 15 children with extrapyramidal syndromes, the central conduction time was normal. Use of brain stimulation for neurosurgical monitoring Although somatosensory motoring has been shown to be of use during neurosurgical procedures to alert the surgeon to the

 possibility of cord damage, the use of motor monitoring is far more relevant because paraplegia is one of the most feared, although rare, outcomes of surgery near the cord. Electrical brain stimulation and recording from the cord by epidural electrodes have been achieved; responses consist of a series of waves analogous to the D and I waves recordable in primates. Magnetic stimulation appears to produce I waves but the responses are very sensitive to anaesthetic agents and the depth of anaesthesia produced, especially nitrous oxide. Monitoring of motor tracts during surgery is best achieved using electrical brain stimulation and is often combined with somatosen- sory evoked potential monitoring. FURTHER READING Chen R, et al. (2008). The clinical diagnostic utility of transcranial mag- netic stimulation: report of an IFCN Committee. Clin Neurophysiol, 119, 504–32. Magistris MR, et al. (1999). A clinical study of motor evoked poten- tials using a triple stimulation technique. Brain,122 (Pt 2), 265–79. Mills KR (1999). Magnetic stimulation of the human nervous system. Oxford University Press, Oxford. Rothwell JC, et al. (1991). Stimulation of the human motor cortex through the scalp. Exp Physiol, 76, 159–200.

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