Functional study technologies of the central nervous system (CNS) are fast developing, yielding further objective data for evidence based neurological rehabilitation. Transcranial magnetic stimulation is a safe and non invasive technique of functional investigation of several aspects of the CNS. During the past few years many studies have focused on motor evoked potentials (MEPs) in the investigation of central nervous system and particularly of central motor pathways. Among the various issues of rehabilitative concern in this context, the prognostic value of MEPs of motor outcome after stroke is the most interesting one. The aim of this review, conducted on Medline database, is to find out the current agreement in the literature about this topic and to outline clinical criteria of use of the test. Many of the retrieved papers suggest an added value of MEPs on motor prognosis after first ischemic sylvian stroke, highlighting higher specificity in clinical cases with paralysis or severe paresis in the acute stage. A clinical use of MEPs in specific stroke subgroups might help to plan a more individual rehabilitative project through realistic motor recovery goals and selected techniques of treatment; a more reliable motor prognosis may also be useful for rehabilitation effectiveness research and for a more aimed use of resources.

Key words: Cerebrovascular accident - Evoked potentials, motor - Magnetics - Prognosis - Rehabilitation.

The recent and fast developing new technologies of the central nervous system (CNS) functional study supply neurological rehabilitation research with further objective data.

Transcranial magnetic stimulation (TMS) is a non invasive and safe technique of investigation of the CNS and, in particular, of motor pathways evoking motor potentials in muscles. During the last 10 years, TMS research has greatly developed yielding, besides other aspects of study of the physiology and pathology of the CNS, several issues of specific interest for the physiatrist; on the other hand, the search for objective assessment tools in important CNS diseases to work out more accurate individual prognosis, better plan rehabilitation program and spare resources, is mandatory.

The study with TMS after stroke is one of the most interesting and promising topics; in particular the predicting value of motor evoked potentials (MEPs) on motor outcome has been focused on by many authors and seems to collect nowadays widespread agreement even if the employment criteria are not enough cleared yet.

Moreover, MEPs studies have investigated further issues in the management of post-stroke patients such as spasticity, motor neglect and assessment of subclinical cases.

The aim of this study, after a brief description of the technique and of the most common clinical and
research uses of rehabilitative interest, is to review the literature about early prognostic value of MEPs on motor outcome after stroke, highlighting agreement about which stroke subgroup may more clearly benefit from this neurophysiological test.

The bibliographic computer-aided search was made by means of Medline database, using the flowing key words: motor cortex, stroke, motor evoked potential, transcranial magnetic stimulation, rehabilitation and prognosis. The selection of the studies was accomplished observing a major hierarchical evidence criterion and the search was limited to the last 10 years.

**Technical features of transcranial magnetic stimulation**

The possibility to stimulate the cortex with magnetic fields and particularly the motor area in order to get information about motor pathways of the CNS, is well known since early 1980;5 previous attempts, using electrical stimulations that produce deeper effects and cause more discomfort, were abandoned. Magnetic stimulating coil, placed in contact with the skull, expose the cortex to a transient magnetic field that induces electric currents. When cortical neurons attain the needed threshold of depolarization, an action potential is generated; if the motor cortex is stimulated, an efferent volley starts and MEPs can be recorded by surface electrodes in muscles in the contralateral limbs. The standard technique lacks of spatial precision allowing a regional stimulation even if, when needed, more focal coils are now available. The MEPs usually studied parameters are: threshold of stimulation, latency, amplitude and central motor conduction time (CMCT). CMCT can be calculated stimulating the CNS at different levels and working out the time difference or employing the F wave method subtracting the peripheral time to the compound MEP latency. Data are usually collected at rest and during a slight voluntary contraction of the target muscle, recording normally in this last condition MEPs of shorter latency and wider amplitude. Further, MEPs recorded with facilitation allows the study of the silent period, the time of physiological period of EMG inhibition after the MEP.

MEPs give information about the integrity of central motor pathways and about the excitability and topography of the motor cortex even if the presence of peripheral neuropathies or associated pathology of the CNS can limit the amount of useful data available.

The TMS technique is painless and with few contraindications such as the presence of cardiac pacemaker or metallic fragments and implanted devices in the head or in the neck; a low risk of seizures has been reported and the technique has been judged as relatively safe.2

**Clinical and research use**

The TMS has been employed in the study of motor pathways in various CNS pathologies such as cerebrovascular, demyelinating, spinal cord diseases, movement disorders and in the study of the CNS plasticity and recovery after cerebral injury or vascular damage.

In particular, as far as stroke is concerned, the predicting value of MEPs on motor outcome has been focused on by many authors. Studies about changes of the silent period, being a parameter depending on motor cortex excitability, have suggested the possibility to get objective information about the degree of spasticity,3 his occurrence 4 and the assessment of motor neglect.5 Further, studies on motor subclinical cases after minor stroke have been done, showing good sensibility of the technique.6, 7

Mapping studies of the motor cortex using focal coils have shown regional cortical plasticity phenomena during motor recovery after stroke;8 further, neuroplasticity produces MEPs changes still present many years after stroke.9 These studies are consistent with previous works on animals, functional neuroimaging data and have recently yielded information too about treatment induced cortical plasticity.10-13

Recording of ipsilateral MEPs in the paretic limbs has arisen new questions about the unmasking of uncrossed motor pathways, the value of this finding on motor recovery 14-16 and the onset of mirror movements.17

Moreover, in recent years, a new issue of investigation has developed with the technical possibility of repetitive TMS and its possible use as a therapeutic tool in the treatment of various diseases such as depression and other diseases; repetitive TMS has been also employed as a research neurophysiological tool to short-term disrupt focal cortex functions in order to study cortex plasticity phenomena or even induce plasticity itself after cerebral damage.18
The predicting value of motor evoked potentials on motor outcome after stroke

A reliable tool for predicting functional and motor outcome after stroke would be of great help to better plan a rehabilitative individual project, assess therapies, spare resources and give more precise information to patients and care-givers.

Kwakkell et al. 19 reviewed the literature for studies on predictors of functional outcome after stroke; the authors found out major evidence for age, previous stroke, urinary continence, consciousness at onset, disorientation in time and place, severity of paralysis, sitting balance, admission ADL score, level of social support and cerebral metabolism but highlighted, heterogeneity and flaws in research methods. Further, most of these works used in the follow up ADL assessment scales such as Barthel index, focusing on functional outcome as a result of motor CNS recovery and adaptation.

Size and location of the stroke, assessed by CT or MRI, can also give information about motor prognosis 20 but fail in early ischemic lesions detection and lack the possibility to functionally motor pathways. 21 The possibility of TMS of directly investigate motor pathways after stroke has been exploited by many authors looking for the possibility of both predicting motor outcome and better understanding CNS recovery process. In particular MEPs are reported to give early information about residual integrity of corticospinal tract 22 with major specificity of clinical evaluation alone in the acute phase when the presence of edema and diaschisis phenomena accounts for initial more severe motor conditions. As far as subcortical stroke is concerned, MEPs prognostic value on hand motor outcome in the acute stage seems to be more specific on hand strength then on dexterity recovery 23 which, on the contrary, is suggested to be more dependent upon postacute cortical reorganisation and upon associated sensory loss.

The retrieved studies included patients with cortical or subcortical first ischemic sylvian stroke excluding, besides patients presenting technical contraindications, cases with a poor survival prognosis or pre-existing impairments of the upper limbs; MEPs were normally recorded on upper limbs on both sides during the first week after stroke and assessment of motor and functional recovery was generally made with clinical and sometime neurophysiological follow-up to a 12 months period.

The more widespread interest in MEPs prognosis of hand motor recovery depends, besides the great rehabilitation importance, on the more strict relation with the corticospinal tract integrity 24, 25 which is directly investigated with MEPs. Heald et al., 26 presenting the greatest number of patients assessed, reported a better recovery process and a lesser mortality throughout a year when MEP was present and normal CMCT compared with cases with delayed CMCT and particularly with cases absent MEP. Escudero et al. 27 reported a prognostic value of recording MEPs in the acute stage with normal CMCT particularly when patients presented a severe initial paresis and regardless to the initial conditions of Barthel scores. Several studies have confirmed the prognostic value of the presence of MEPs in the acute stage finding out the amplitude and CMCT as the most important parameters. 25, 26-30 Amplitude has been shown to be of major interest, along with CMCT and threshold, particularly when expressed as percentage of the amplitude of motor potential obtained with troncular peripheral stimulation 31 yielding, according to the author, a prognostic information higher than neuroimaging and clinical assessment. Catano et al. 32 suggested the only early presence or absence of MEPs being a useful prognostic datum, highlighting the importance of the facilitation technique. A higher threshold of stimulation, showing a lower cortical excitability, has been reported as a useful prognostic indicator when MEPs were executed within the first 8 post-stroke hours. 33 Further, some authors demonstrated a close relationship between motor and neurophysiological recovery showing progressive improvement of MEPs parameters or the appearance of previous absent potentials 25, 29, 31.

Looking for an equal motor condition on the initial observation in order to better differentiate motor recovery, many authors used among the inclusion criteria a condition of complete hand palsy in the acute stage of first ischemic stroke of middle cerebral artery area. 22, 34-36 These works agree to confer to the early absence of MEPs a predicting value of absent or poor hand motor recovery, suggesting also a correlation between MEP amplitude in the early stage and Medical Research Council and Barthel scores 14 days after of stroke. 35 On the other hand few authors didn’t find out ev-
evidence of prognostic value of MEPs but including in one case in the sample both ischemic and hemorrhagic cases; another author found out MEPs and somatosensory evoked potentials of limited value in the acute stage in predicting motor recovery.

Few studies investigated the chronic changes of MEPs: patients who had a good motor recovery assessed many years after subcortical stroke, kept on showing changes in MEPs parameters as a result both of persistent motor pathways damage and of cortical reorganisation.9

Finally, a recent systematic review, selecting 5 among 85 studies, has shown evidence of the prognostic value of MEPs on motor and functional recovery, finding more consistent data when a paralysis or a severe paresis were present, although a meta-analysis was not possible owing to the clinical heterogeneity of the studies; the authors, reporting in these cases a high specificity of the test although along with a relatively low sensitivity, suggested a selected clinical use of MEPs.

The study of the lower extremities has arisen less attention both for the more difficult detection of MEPs and for minor critical aspect of recovering skilled movement for functional goals. The retrieved studies about this item suggest a predictive value of MEPs, recorded from tibialis anterior muscles, on motor recovery of lower limb but not on disability recovery, in patients with initial paralysis.40, 41

Discussion and conclusions

Clinical and neuroimaging assessments give important information about prognosis of motor recovery after stroke. On the other hand MEPs seem to yield early useful complementary data about integrity of corticospinal tract which is most responsible of the post-stroke early phase of motor recovery in particular as far as strength is concerned; this stage, during which the most significant intrinsic recovery may occur and the effectiveness of rehabilitation is higher, is initially based upon the resolving process both of edema, diaschisis phenomena and of the recovery of ischemic penumbra which may account for a more severe initial clinical condition.

The early MEPs assessment of integrity of fast motor pathways may allow a better planning of individual rehabilitative program and an optimisation of resources. In selected patients this test, showing sparing of the corticospinal tract, might besides help avoiding phenomena such as learned nonuse syndrome likely along with sparing of functional loss of movement representations near the ischemic area. In these cases the test may suggest the prevailing use of intrinsic recovery techniques of the affected limb rather than a compensatory rehabilitation. On the other hand, intrinsic motor recovery techniques like constraint-induced therapy are able, as demonstrated by TMS focal studies, to enlarge the specific motor cortical output area.

Even if changes in MEPs parameters occur also in the subacute stage, suggesting interfering multiple neurological factors, and may persist after complete motor recovery, MEPs seem to have less sensitivity in the prediction of motor recovery when executed during the post-acute phase. This recovery stage depends more in fact, beyond adaptation phenomena, upon slower neuroplasticity events that account for achieving a higher level of movement complexity such as dexterity and coordination. These issues are now studied by researchers by means of functional neuroimaging and TMS mapping, yielding a further basis for stroke rehabilitation planning.

In conclusion, even if there are great differences in study methods regarding technical, initial motor impairment degree and followup planning, our review shows widespread agreement on considering MEPs a reliable tool to predict motor outcome after stroke supplying added information to clinical and neuroimaging data. In particular, many authors agree that a clinical use of MEPs for the highly specificity prognostic value on motor outcome can be suggested when paralysis or severe paresis is present in the early stage or when cognitive impairment and lack of cooperation do not allow reliable clinical assessment.

MEPs after stroke could also be an evaluation tool of rehabilitation therapies; in patients with initial severe post-stroke motor impairment in the acute stage, a better distinction of prognostic subgroups can be useful in rehabilitation trials to work out the effectiveness of additional sensorimotor stimulations.

Further studies are required both to improve MEPs sensitivity in post-stroke subgroups with initial upper limb paralysis and to better understand the clinical importance of the test in paresis subgroups; more
aimed works are moreover necessary to improve the knowledge about the MEPs prognostic value in lower limbs motor recovery.

References


