Transcranial Magnetic Stimulation and Transcranial Electrical Stimulation in Horses

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Transcranial Magnetic Stimulation and Transcranial Electrical Stimulation in Horses

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KEYWORDS

• Horse • Transcranial stimulation • TMS • TES • MEP • Neurology • Ataxia

KEY POINTS

- Transcranial MEPs offer a valuable ancillary non-invasive test to assess the integrity of the motor function of the spinal cord in horses.
- Are complementary to radiological imaging techniques revealing the anatomy of the spine and spinal cord.
- Their high sensitivity for minor impact on the spinal cord likely exert the diagnostic power to also low grades of ataxia.
- Dominant late MEPs of extracranial elicited startle reflexes are characteristic for horses.
- MEPs of muscles from different segmental levels can likely be used to locate spinal cord lesions with affected motor functions

Abbreviations	
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
MEP	(muscle) motor evoked potential
MT	motor threshold
LMN	lower motoneuron
EDM	equine degenerative myeloencephalopathy
EPM	equine protozoal myeloencephalitus
CVSM	cervical vertebral spinal myelopathy
ECR	musculus extensor carpi radialis
TC	musculus tibialis cranialis

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INTRODUCTION

Depending on the localization of the lesion, spinal cord ataxia is the most common type of ataxia in horses. Most prevalent diagnoses include cervical vertebral stenotic myelopathy (CVSM), equine protozoal myeloencephalitis (EPM), trauma and equine degenerative myeloencephalopathy (EDM). Other causes of ataxia and weakness are associated with infectious causes, trauma and neoplasia. A neurologic examination is indispensable to identify the type of ataxia. In addition, clinical neurophysiology offers tools to locate functional abnormalities in the central and peripheral nervous system. Clinical EMG assessment looks at the lower motoneuron function (LMN) and is used to differentiate between neuropathy in peripheral nerves, which belong to LMNs and myopathy.[1] As LMNs reside in the spinal cord, it is possible to grossly localize lesions in the myelum by muscle examination.[2] Transcranial (tc) stimulation techniques are gaining importance in all areas of medicine to assess the motor function of the spinal cord along the motor tracts to the LMNs. Applications in diagnostics, intraoperative neurophysiological monitoring (IONM), and evaluation of effects of treatment are still evolving in human medicine and offer new challenges in equine medicine. Tc stimulation techniques comprise transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES). TMS was first applied in horses in 1996 by Mayhew and colleagues[3] and followed by TES. The methods are exchangeable for clinical diagnostic assessment but show a few differences.

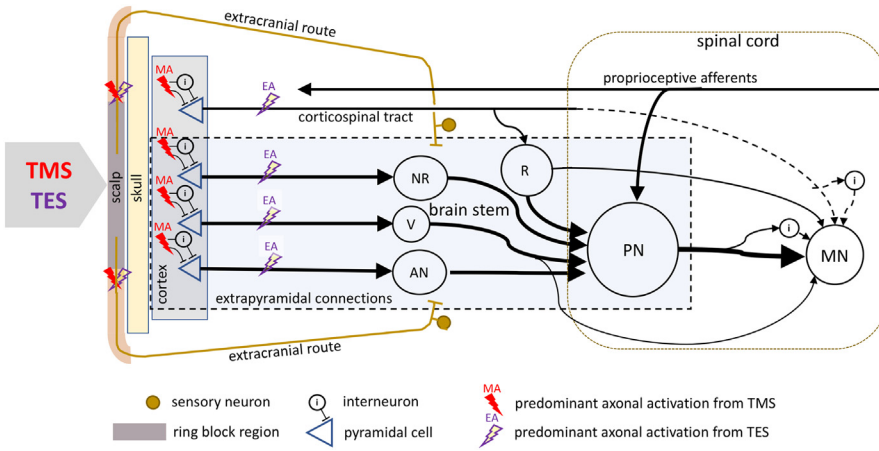

Fig. 1. TMS and TES activation of important motor tracts as expected in ungulates as horses. The scheme is speculative because no specific anatomic data on horses is available. The predominant intra and extracranial locations whereby axons are activated are indicated. When stimulation intensities increases, activated (EA) locations will shift toward the brain stem while TMS activation (MA) remains in place in the cortex. Extracranial activated sensory axons are conveyed to the neural network in the brain stem whereby startle reflexes may be elicited. The proprioceptive nucleus PN (C3-C4 levels) has a major integrating role in the depicted motor tracts and proprioceptive afferents. R, reticular neurons; NR, nucleus ruber; V, vestibular nuclei; AN, additional nuclei like the tectum; MN, motoneuron. The PN possibly also receives collaterals from corticospinal tracts. Retrograde connections of the PN to the brain stem and cerebellum are not shown.

PRINCIPLES OF TRANSCRANIAL STIMULATION, CONNECTING NEURAL CIRCUITS, AND MUSCLE MOTOR-EVOKED POTENTIALS

In horses, TMS and multipulse TES are interchangeable transcranial stimulation techniques suitable to assess the motor function of the spinal cord.[4] Elicited muscle motor-evoked potentials (MEPs) reflect the functional properties of neural elements of the route along brainstem nuclei, extrapyramidal motor tracts, propriospinal neurons, and motoneurons. Both techniques are applied to standing sedated horses, are painless and noninvasive.

Fig. 1 gives a schematic survey of which and whereby axons are activated and their routes across the brain stem and spinal cord to the motoneuron. TES and TMS share many neurophysiological properties. Small differences are attributable to dissimilarities in the interaction with the brain.

TMS generates induction currents in the brain from a magnetic coil placed on the forehead of the horse. These mainly activate axons in the cortex that in turn activate cascaded neurons of which the pyramidal cell or upper motoneuron is the end station in the cortex and gateway to the spinal cord. The pyramidal axons form the corticospinal tract and propagate a train of action potentials further down the spinal cord. These can epidurally be recorded as dominant I (indirect)-waves.[5,6] A few corticospinal axons may also become activated of which small D (direct)-waves may join.

In contrast to TMS, TES activates mainly corticospinal tract axons directly near the active anodal electrode.[6,7] This occurs below the cortex bypassing the cortical neurons. These action potentials can be recorded downstream as a large dominant D-wave. Cortical axons are activated as well and appear as subsequent repetitive relatively small I-waves. I-waves are extra attenuated or absent under sedation. The insensitivity of D-waves for anesthetic agents is an important reason why TES is used instead of TMS in IONM in humans. The predominant D-waves of TES become evident as shorter motor latency times (MLT) of muscle MEPs than in TMS whereby I-waves are predominant.[5,8–12]

Latency times of muscle MEPs are the sum of central and peripheral conduction times. Delayed latencies may also have a peripheral origin. The conduction time between nerve root and muscle must be subtracted from the muscle MEP latency to obtain the pure central motor conduction time (CMCT) between the stimulated brain and spinal motoneuron. Peripheral conduction times for correction are obtained by direct stimulation at nerve roots or from latency times of M- and F-waves of MEPs from peripheral nerve stimulation.[13–15] The CMCT specifically reflects the motor function of brain and spinal cord. An often-used term of “upper motoneuron function” is, strictly taken, incorrect as the pyramidal tract is not exclusively involved as extrapyramidal tracts also contribute to the generation of muscle MEPs.

APPLICATIONS OF TRANSCRANIAL STIMULATION IN HUMAN MEDICINE

TMS and TES provide information about the motor functions and the modulating effects of the cortex, subcortical nuclei and nuclei in the brain stem, cerebellum, and spinal cord.[14] This led to applications in areas of medicine and neuroscience, unfolding of tools for clinical diagnostic assessment like stroke, cervical myelopathy, amyotrophic lateral sclerosis (has similarities with EDM in horses), dystonia, Parkinson’s disease and cerebellar ataxia,.[14,16–18] Neurophysiological measures as corticomotor threshold (MT), MEP amplitude, latency and wave morphology, cortical silent period duration or CMCT among others, can provide evidence of disease-related changes in motor cortical control output in patients. Repeated TMS (rTMS) is also considered in the treatment of many disorders in neurology and psychiatry like motor disorders such

as dysphagia, anxiety and PTST, depression, neuromodulation of pain, neurologic, and psychiatric diseases.[19–21] Intraoperative neurophysiology is a specific field whereby transcranial MEPs are used in which TES is pivotal. TES has a recognized place in the fast-expanding applications for IONM and surgical and anesthetic interventions like for example, in the placement of spinal or deep brain stimulation electrodes and neuronavigation.[14,22]

In humans, TMS is used for clinical diagnosis as it is painless. Frequently used muscles for the assessment of the motor function of the spinal cord are hand muscles, extensor carpi radialis, and biceps in the upper limbs and the anterior tibial, gastrocnemius, and abductor halluces muscle in the lower limbs.[15,23,24] Intercostal and paraspinal tc-muscle MEPs can be used to determine the location of the lesion responsible for the thoracic myelopathy. Such MEPs can identify the level of origin of a myelopathic lesion in patients with a radiologically visible lesion.[25–27] Also accessible by TMS are facial, tongue, respiratory, laryngeal, pharyngeal, cricothyroid, vocal cord, pelvic, and anal sphincter muscles.[14,24,28–32]

The CMCT is correlated with the grading of myelum compression on MRI and with the degree of functional involvement of the spinal cord as observed by a neurologic examination. TMS has a sensitivity and specificity of 100% and 84.5% to detect cord compression and might even detect subclinical lesions.[18,33] TMS may clarify whether locations with anatomic cord compression as found in MRI are a functional lesion.[34–36] MEP studies can demonstrate spinal involvement even when radiological evidence for spinal cord damage is absent or equivocal.[17] Muscle MEPs allows to monitor progressive diseases. Pre, per and postoperative testing monitors neurophysiological events during surgery and reflects the status after surgery.[16,37,38] Tc muscle MEPs provide no information about the etiology of the lesion.[16]

TRANSLATIONAL ASPECTS OF HUMAN APPLICATIONS IN EQUINE MEDICINE

Many applications of transcranial MEPs in human medicine can be transposed to equine medicine. Transcranial stimulation is a valuable ancillary test to assess the integrity of the motor tracts in horses. The technique is painless and safe and shows good sensitivity to detect lesions along the descending motor pathways when used under sedation to prevent anxiety and occasional kicking.[39,40] When horses are sedated, the discomfort of TES and TMS is comparable while both techniques can grossly be considered as interchangeable.[4,41,42] In man and animals with spinal cord trauma and ischemia, TMS has proven to be a valuable diagnostic tool for the detection of lesions along the spinal cord.[43–46] TMS and TES are valuable to detect abnormal MEP characteristics at different grades of ataxia in horses.

So far, only prolonged MLTs muscle MEPs of thoracic and pelvic limbs are used and described. The large inter-stimulus variations of MEP amplitudes make these still useful but are of limited value.[39,40,42,47,48] Further diagnostic improvements and applications are expected by including more muscles.

The pure CMCT reflects specifically the motor function of the spinal cord and results from the subtraction of the peripheral nerve conduction time from muscle MEP latency. The peripheral conduction time can be determined from M and F responses or obtained by nerve root stimulation.[13,14,24]

Tc-MEPs of paraspinal muscles can be used to localize spinal cord lesions with a segmental accuracy. Other interesting muscles for the assessment of their functional integrity and innervation are facial, pharyngeal, vocal cord, and other muscles that are innervated by cranial nerves, respiratory muscles, pelvic muscles, and anal sphincters. Urination, defecation, and sexual functions depend on the anatomic and

functional integrity of central and peripheral nerve pathways to the pelvic floor and the sacral region. TES may be an attractive alternative for the assessment of facial muscles to avoid coil repositioning errors and saturation effects of physiologic amplifiers caused by strong induction currents in close proximity to a TMS coil.

IONM modalities can be transposed to horses. Challenging application are IONM in spinal cord and nerve root decompression, placement of baskets, and stabilization of the spine. Sensory evoked potentials can be of complementary value. However, IONM may limit the choice of anesthetic agents.[22] Other potential applications are the assessment of the progression of symptoms and functional recovery on treatment of prognosis.

Neural Pathways from Cortex to Spinal Motoneurons

Spinal motor tracts have crossed and uncrossed connections to the spinal cord. When asymmetry exists in muscle MEPs, their lowest MTs are found at the contralateral side of the active electrode or active induced cortical current direction. The crossed corticospinal tract has a dominant role in the voluntary control of movement in man, but is less important in phylogenetically older species[49] whereby extrapyramidal pathways and associated neuronal circuits exert a major role. An outline of the main connections from literature data is given in **Fig. 1**, which depicts the dominating connections from the brain stem to motoneurons. This model is speculative because no specific anatomic data on horses is available. Although differences may exist between rodents, cats, rats, and ungulates, such as horses, it is expected that these animals share the integrating and dominating role of the proprioceptive neuron (PN) in the control of movements. Most experimental studies are performed on cats and rodents. The next outline is mainly based on studies performed on cats of which most experimental studies are published and used as a reference for horses. The reticulospinal, rubrospinal, tectospinal, and vestibulospinal tracts are important brain stem and mesencephalon leaving extrapyramidal motor tracts and are a prominent input to C2-C4 spinal PNs.[50] The PN is an important common path station. However, also direct monosynaptic connections of vestibular nuclei to motoneurons of extensor muscles of the knee are reported in cats.[51] It relays to cervical and thoracic motoneurons and back to the brain stem and cerebellum.[50,52,53] Monosynaptic connections between the nucleus ruber and motoneurons are also encountered as shown in **Fig. 1**.[54] Collateral connections of the corticospinal tract with reticular and other neurons in the brain stem provide an access port to the PN. The PN is also an important interacting station with somatosensory axons of which many are of proprioceptive origin. These exert a modulating influence on the control of movements and also on tc-MEPs.

Selective studies with epidural measurements at supramaximal TES or TMS and stimulation in the brainstem reveal that the major portion of the extrapyramidal motor conduction runs along the reticulospinal and vestibulospinal tracts in the ventral funiculus.[55–58] Tectospinal fibers are there less numerous and share the ventral funiculus until C4 level.[55] The rubrospinal pathways in cats play probably a minor role in the spinal MEPs from TMS.[57,59]

Most studies in older species show a large variety of connections via the PN and interneurons to motoneurons. The pyramidal tract is likely not a significant motor pathway (dashed connections in **Fig. 1**). It is generally accepted that the pyramidal pathways descend to the level of the first cervical segment in the horse.[60] For example, the locomotion in rats is not affected by further caudally created lesions.[61] It is presumed that the rise of the membrane potentials of LMNs after transcranial stimulation is mainly controlled by transmission through PNs, while a monosynaptic transfer via the pyramidal tract is subordinate or absent.

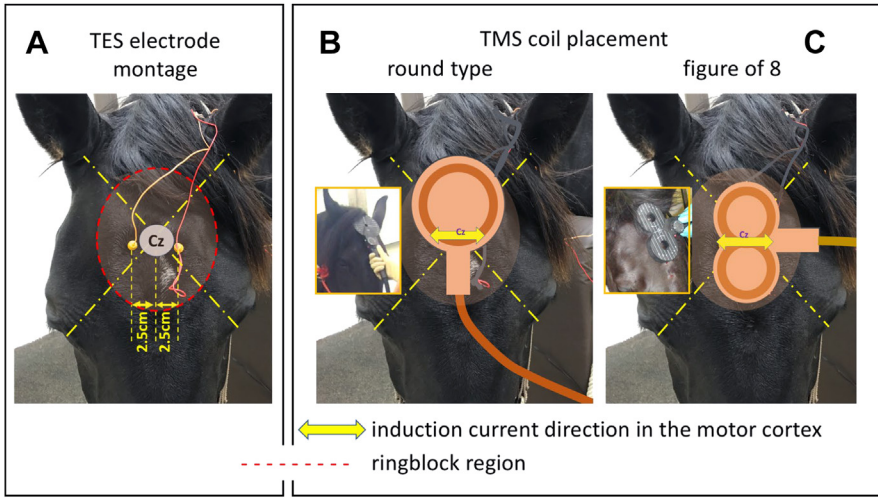

Fig. 2. Optimal montage of TES electrodes (*A*), positioning of a round TMS coil (*B*) and a butterfly or figure-of-8 TMS coil (*C*) over the head of a horse. The shown locations and given coil orientations provide the induced current direction (*B*, *C*) to focus on for lowest stimulation thresholds. The optimal currents direction in the cortex runs is centered between the vertex Cz (crossing point of dashed *lines* connecting eye and contralateral ear) and about 1 cm frontal from Cz. The corkscrew or s.c. needle electrodes are bilateral placed on a distance of about 2.5 cm from the midline (see Fig. 2A). Round coils produce circular currents while butterfly coils currents are focused between the double coils. The dashed circle indicates the location of the ringblock.

Remarkable is the large variety in conduction velocities of different motor tracts in cats. Conduction velocities in the corticospinal tract are around 60 to 70 m/s.[56,59,62] These are markedly higher in all extrapyramidal tracts with the largest velocities in the vestibulospinal and reticulospinal motor tracts in the ventral funiculus with upper ranges of respectively 164 m/s and 140 m/s.[51,56,58,63–65] This indicates that transcranial MLTs are ruled by the ventral located vestibulospinal and reticulospinal tracts.

GUIDELINES FOR TRANSCRANIAL STIMULATION

TES Electrode Montages and TMS Coil Placement

Lowest transcranial MTs are obtained by applying currents in the motor cortex in a lateral direction over the vertex Cz or a little more frontal. For TES, corkscrew or s.c. needle electrodes are bilaterally placed at a distance of about 2.5 cm from the midline (**Fig. 2**A). TMS can be performed by round (**Fig. 2**B) or figure-of-8 (butterfly) coils (**Fig. 2**C). More focal stimulation is possible with a figure-of-eight-shaped coil.[66]

Induction currents in the cortex from the changing magnetic field should run in the lateral direction as shown. Round coils produce circular currents within the rim while butterfly coils currents are focused between the double coils. When Cz is within about 1–2 cm from the frontal external edge of the round coil, the situation agrees with the optimal location nr 2 in the paper of Nollet.[67] With a typical 12 cm diameter round coil the strength is halved at 4–5 cm from the coil surface.[68] The cerebral cortex is about 1–2 cm separated from scalp surface. TMS-induced currents are severely attenuated at deeper locations of the basal ganglia or thalamus.[69] Maximum (100% intensity) magnetic field strength changes in TMS pulses are 35 to 41 kT/s for butterfly (2 × 75 mm) and round coils (~120 mm).

The shape of the TMS coil has practical consequences. The induced current direction of a round coil is defined by the coil surface, which touches the skin. The orientation of the coil handle has no relevance. In contrast, the handle of a butterfly coil points in the current direction. Its orientation is highly relevant and must keep constant to secure stimulation conditions. The current direction in the brain can be reversed by rotating the butterfly coil 180° with the handle in the opposite lateral direction. Both coil types can be used for diagnostic TMS. A nonfocal large round coil is preferred as its positioning over the target region is easier and less susceptible to minor changes in the coil position and activates a larger cortical area and depth which is important for the activation of deeper-seated primary motor areas of pelvic limb muscles.

STIMULATION PARAMETERS

TES and TMS pulses can be monophasic or biphasic. In humans, transcranial monophasic pulses deliver asymmetric MEPs and MTs when the currents in the brain run in the lateral direction. The lowest TES MTs are found at the anode,[7,9,70] which is the active stimulation electrode for muscle MEPs on the contralateral side. Biphasic transcranial pulses deliver symmetric MEPs and MTs. Asymmetry of muscle MEPs and MTs of monophasic pulses are not reported in phylogenetic older species like rodents, cats, and ungulates.

Widths of monophasic and biphasic TMS pulses are about 100 to 150 μs and 200 to 280 μs.[69] TMS in horses is mostly performed with monophasic pulses of a Magstim 200 (Eden Prairie, MN USA) stimulator at maximum intensities of 100%.[47,69,71] These are supramaximal levels whereby MEPs are symmetric anyway. Also biphasic pulses from a MagPro Compact magnetic stimulator (Medtronic Functional Diagnosis A/s) are used.[4] Published TES studies in horses are performed with 3 high biphasic pulses with 100 μs/phase pulse width and 1.3 ms interpulse interval.[41,72]

Transcranial muscle MEPs of different muscles may have different MTs.[14,24] These depend on the distance between upper motoneurons and TES electrode or TMS coil.

MUSCLE MOTOR-EVOKED POTENTIALS

Transcranial MEPs

Both TMS and TES generate trains of action potentials at the entry of descending motor tracts to motoneurons of muscles whereby MEPs are recorded. Motoneurons fire earlier at higher intensities while latencies decrease. The reduction of latencies for maximum TMS intensities is in dogs maximal −2.5 ms.[73] Stimulation by 3 high multipulse TES pulses, give an extra boost for earlier firing. Increasing TES intensities penetrate deeper in the brain. This shortens the motor route length and MLT. In humans, the latency time of D-waves is decreased to about −0.8 ms at the depth of the cerebral peduncle[10,74–77] and −1.8 ms at the foramen magnum.[78,79] At about 3 times the transcranial MT the D-wave amplitude increases by 100% to 200% as D-waves of extrapyramidal spinal motor tracts join the corticospinal D-wave.[80] The distance between vertex and brainstem of horses and cats is shorter than in man which is expected to cause smaller differences between (sub)cortical and brainstem thresholds. This is also reflected in the feline experiments of Konrad and colleagues[56] and Kawai and colleagues[59] whereby the supramaximal intensity level for the direct stimulation of the extrapyramidal tracts in cats lies close to the TES threshold to the brain stem but may exceed the depth range of TMS. This may introduce differences in muscle MEPs between TMS and TES.

Reported equine intensity-dependent of muscle MEP MLTs decreases around −1.7 ms and −2 ms for TES for increases of stimulation intensity of respective 20% and 20V above MT.[4,42]

Sedatives may suppress the synaptic transmission to motoneurons.[81–85] This can be compensated by multipulse stimulation.[4,86]

Extracranial Elicited Reflexes

A recently unfolded unique phenomenon in horses is the occurrence of late MEPs below transcranial MTs. These appear about 15 to 20 ms later than transcranial MEPs as a prominent part of muscle MEPs.[4,41,42] The late MEPs in all muscles impress as extracranially elicited startle reflexes (SR). Since these appear below transcranial MTs, these SRs originate most likely from the activation of extracranial sensory afferents as shown in **Fig. 1** and conveyed to the brain stem and spinal cord.[41] The difference between transcranial and late muscle MEPs latencies defines a transcranial time window for which the transcranial MEP is free from interference with late MEPs.

Muscle motor-evoked potential recording

Muscle MEPs are preferably measured by extramuscular electrodes as these observe the elicited electrical activity of many muscle fibers. Intramuscular needle electrodes record the activity of only a few muscle fibers can easily dislodge and impair reproducibility. However, these are still needed for deep-seated muscles.[48] Signals from subcutaneous needle and gelled surface electrodes are highly correlated. The signal quality is good when impedances are low. However, the signal quality of surface electrodes is unpredictable and may show a high background noise, which depends on the electrical properties of the skin which can be dry or wet and may contain salty debris.[48,87] Taping of both electrode types is recommended for the fixation and improvement of the signal quality but surface electrodes may show long adaptation times.[87] Subcutaneous needle electrodes are recommended as these have a predictable good signal quality. Adhesive surface electrodes are a useful alternative choice.

Segmental conduction times and velocities of paraspinal muscle motor-evoked potentials

Transcranial MEPs of paraspinal muscles can be used to determine the focus of myelopathic lesions with a segmental precision. This has been shown in humans in patients with a radiologically visible lesion.[25–27,88] Surface recordings of paraspinal muscles may be confounded by cross-talk from underlying fascicles.[89] Most appropriate are intramuscular needle or hookwire electrodes.[90] Clinical applications of paraspinal muscle MEPs in horses are not reported yet.

The mono-segmentally innervated multifidus muscle interconnects 2 subsequent vertebral bodies.[91] Other paraspinal muscles may be multisegmentally innervated which could blur the segmental accuracy.

Placement of intramuscular electrodes in the multifidus muscle in horses requires ultrasound guidance by a trained physician with good anatomic knowledge. Hitting nerve roots and blood vessels are potential risks. Paravertebral muscles aside vertebral corpora are easier to access.[92]

The segmental motor latency (SMT) over one segment is equal to the MLT difference over the segment. The SMT is a link in the CMCT chain. The segmental spinal motor conduction velocity (SMV) is defined as the segment length divided by the SMT. The SMT and SMV are suited to identify segmental links with prolonged latencies. Indirectly estimated spinal velocities are well more than 100 m/s.[4] In an unpublished scouting study using multifidus TES-MEP latencies between C3 and C6 levels in 3 horses, we found mean SMVs and SMTs between 141 to 192 m/s and 0.50 to 0.85 ms.

Significant displacement and distortion of the long needle electrodes may result from shearing forces between unequally moving muscle groups and cutaneous tissue

layers. Repositioning of distorted electrodes is not always possible. It is recommended to insert all paraspinal electrodes over a segmental trajectory after finishing the MEP procedure with extramuscular MEPs and use the concluding TES intensity for latency assessment. Multichannel recording allows simultaneous measurements of paraspinal MEPs at single transcranial stimuli.

EQUIPMENT

Transcranial MEPs can be measured with a myograph intended for clinical neurophysiological assessment. Such devices mostly support conduction studies with external TMS stimulators. Build-in peripheral nerve stimulators are not powerful enough for TES. TMS devices can be replaced by an external TES device. The choice of certified TES stimulators is limited. In human medicine, TES is only used in neuromonitoring whereby the stimulator is integrated into most IONM equipment. In the remaining situations, the Digitimer D185 (Digitimer, Welwyn Garden City, UK) stimulator is mostly used as an auxiliary TES device. This voltage stimulator delivers monophasic trains with 50 μs pulse widths and can deliver the required 3 pulses per train with 1.3 ms interpulse time. Although delivered pulse voltages and shapes strongly depend on the impedance of the stimulation electrodes,[93] which affects the accuracy of MTs, the stimulator is reliable for clinical diagnostic use in horses.

A minimal inexpensive configuration consists of a single or 2-channel electromyograph connected to an auxiliary transcranial stimulator. Used myographs in TMS studies in horses are Neurostar, Sapphire, and Synergy (Medelec Ltd, Old Woking UK). These old designs can be replaced by current commercially available alternatives. In human medicine, TES is only used for neurophysiological monitoring with the TES stimulator usually integrated into the IONM equipment.

Single-channel assessment of tc MEPs in horses has practical disadvantages. TES settings need to be read from the stimulator and manually labeled to the MEP traces, which takes extra time. Four-limb assessment requires to repeat the measurements, rewiring, and labeling of muscle electrodes 4 times. This leads to unnecessary stimulations, prolongation of the sedation, and assessment time.

In contrast, to-date multichannel equipment with build-in transcranial stimulators like the NIM-Eclipse (Medtronic-Xomed, Inc USA) can be tailored for diagnostic use in horses. Multichannel MEPs offer the feature for intrastimulus comparisons of MLTs that are insensitive to varying levels of facilitation and sedation,[4,72] enable short-lasting sessions with less discomfort to the horse and don't require manual labeling of MEP traces. As being designed for IONM, the equipment may work cumbersome for diagnostic assessment and is expensive. New applications like segmental motor conduction measurements for locating spinal cord lesions in horses and specific diagnostic protocols for segmental tracing of prolonged SMTs and SMVs require software updates from the manufacturer.

To become attractive for a wide use in equine practice, there remains a need for portable, affordable, and user-friendly equipment, for use by trained equine veterinary practitioners.

SET-UP FOR 4-LIMB TRANSCRANIAL MUSCLE-MEP ASSESSMENT

A general set-up and procedure for 4-limb muscle-MEP assessment will briefly be described with illustrations of applications of TES and TMS with a multichannel and a 2-channel myographic systems in normal horses and a case with ataxia.

After a neurologic examination of the motor function and measurements of the height at withers and weight, horses are prepared for transcranial muscle MEP assessment.

The horses are initially sedated by i.v. injection of a half dose of a combination of detomidine (Detosedan, AST Farma B.V., Oudewater, The Netherlands) and butorphanol (Butomidol AST Farma B.V., Oudewater, The Netherlands). The second half is given before starting the measurement procedure (both 15-20 μg/kg in total).

To minimize extracranial reflexes, a subcutaneous ring block surrounding Cz with a diameter of about 8 cm is placed as shown in Fig. 1A by using 300 to 400 mg lidocaine 2% + adrenaline (Alfasan, Woerden, The Netherlands). For TES, two corkscrew electrodes (Medtronic-Xomed, Jacksonville, FL, Rhythmlink Columbia SC, Natus Medical, Middletown WI) are positioned 2.5 cm bilateral from the vertex at Cz as depicted in Fig. 1A. Corkscrew electrodes cannot dislodge.

Subcutaneous needle electrodes (L 13 mm 27 GA Rhythmlink Columbia SC, Natus Medical, Middletown WI, Medtronic-Xomed, Jacksonville, FL, or other manufacturers) are placed over the musculus extensor carpi radialis (ECR) (10 and 20 cm above the os carpi accessorium) and over the musculus tibialis cranialis (TC) (10 and 20 cm above the medial malleolus) with an s.c. ground needle electrode in the neck. Mono-polar recordings with an active electrode over the muscle belly and a distal located electrode are useful as well. The reference electrode should be placed. Recommended filter settings for high and low pass filters are 50 Hz and 10 kHz.

MEASUREMENT PROCEDURE

After a check of all electrode impedances, confirming correct connections, and background noise checks, repeated MEP measurements are performed by stepwise incrementing stimulation intensities starting at zero intensit with steps of 10V for voltage TES or in TMS steps of 10% from maximum intensity. Measurements are performed twice at each intensity. On the appearance of early MEPs at the first latency jump, measurements may initially show back and forth switching transitions between early and late MEPs in a transcranial segue region. This pattern disappears usually after a few intensity steps when transcranial MEPs remain always visible.

When elicited movements remain acceptable, stimulation intensities steps can be continued to 30V or 30% above the threshold when usually a supramaximal level is approached. Stimulation thresholds of pelvic limb muscles can be one or two intensity steps higher than forelimb or neck muscles because of considerable trial-to-trial variability finally, 6 consecutive muscle MEPs are recorded at the highest intensity step. The shortest latencies associated with the largest amplitude are used for the report.[14,24] For the 2-channel system in one of the presented examples the ECR and TC are first assessed on one side after followed by the assessment of the contralateral side. The second stimulation intensity series can be shortened as transcranial thresholds already are known. For the adaptation of the horse, it is recommended to start at the previously obtained transcranial motor threshold of the ECR and pursuit the series with 10V or 10% steps.

EXAMPLES

Fig. 3 gives an overview of 4-channel recorded MEP responses from the ECR (A and C) and TC (B and D) muscle groups for TES (A and B) and TMS (C and D) in landscape plots. These are illustrative examples from a normal horse without neurologic signs, depicting how MEPs unfold at increasing stimulation intensities. The first elicited

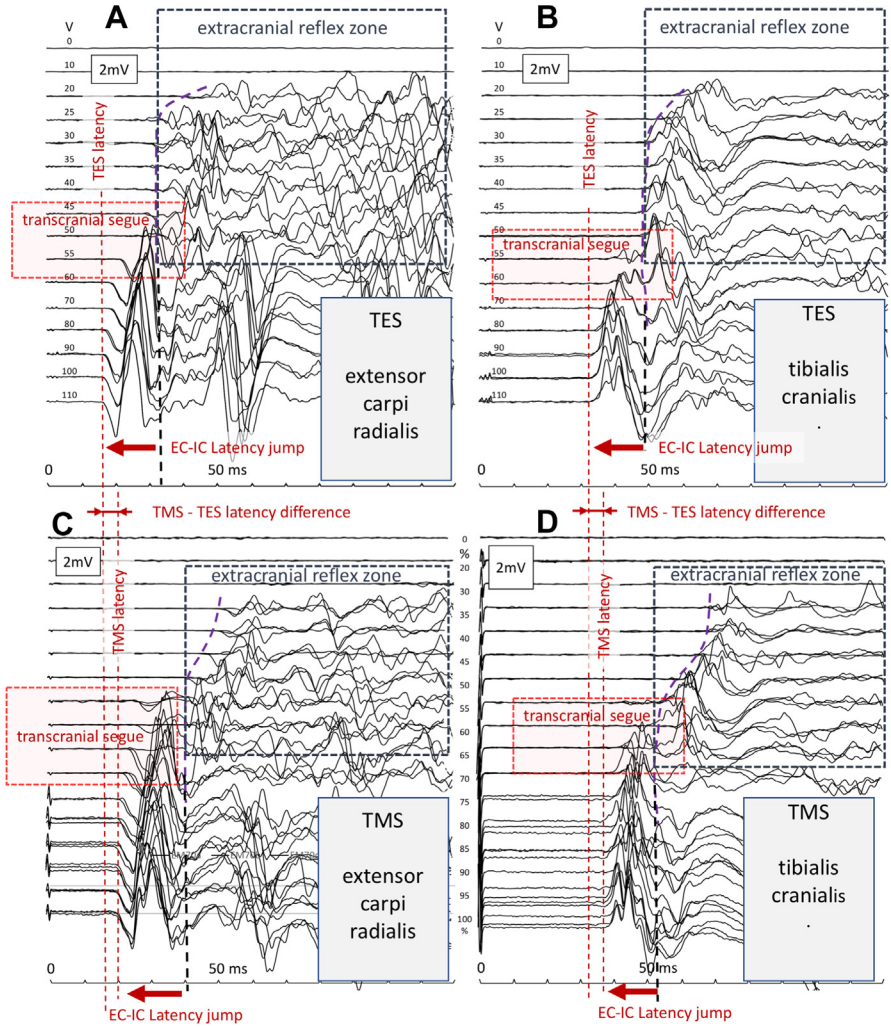

Fig. 3. Overview of MEP responses from the ECR (*A*, *C*) and TC (*B*, *D*) muscle groups for TES (*A*, *B*) and TMS (*C*, *D*) in landscape plots from a normal horse with grade 0 ataxia at stepwise increasing stimulation intensities. The first elicited MEPs are from extracranial origin and show relative long latency times which decrease by about -20 ms when reaching the transcranial thresholds for TES: ECR at about 45 V and TC at 50V and for TMS: at 55% for both muscles. The intensity width of the transcranial segue region is for the ECR 45 to 55V; for TC 50 to 60V for TES or 55% to 70% for TMS. The extra to intracranial (EC-IC) latency jumps are between about -15 to -18 ms. The early latencies of the transcranial MEP then decrease further by about ms.

MEPs are of extracranial origin and show for both TES and TMS relative long latency times at about 45 to 50 ms for the ECR and 65 to 70 ms for the TC muscle groups. These decrease by about when reaching the transcranial thresholds for TES at about 45V and 50V for the ECR and TC or for TMS at 55% for both muscle groups. The intensity range of the transcranial segue region is for TES 45 to 55V and 50 to 60V for the ECR and TC or for TMS 55% to 70% in all limbs. The extracranial to intracranial (EC-IC)

latency jumps are roughly -15 to -18 ms. The transcranial MEP MLTs then decrease further by another -2 ms.

This agrees with the MLT reduction of the APB of −2.3 ms for TMS from rest to voluntary contraction and of the FDI of more than -3 ms for TMS and maximal −1.8 ms for TES for a similar increasing stimulus intensity protocol.[8,9]

The latency jumps define a transcranial time window wherein transcranial MEPs can be analyzed without interference by late extracranial MEPs. The wave shapes and amplitudes of MEPs from TES and TMS in the transcranial window show reasonably good reproducibility.

The latency differences between TMS and TES are about 3 and 3.5 ms for the ECR and TC muscles.

The coefficients of variations (CV) from intrastimulus comparisons are lower than CVs of interstimulus comparison due to the insensitivity to the fluctuating LMN facilitation. Multichannel recordings allow pair-wise intrastimulus comparisons.

TES-MEP Measurements with 2 Channels

An example of a 4 limb TES-MEP assessment with a 2-channel EMG system is given for simultaneous recorded ECR and TC muscles at the right side of a sound horse. The TES intensities are increased by a series of 10V steps. MEPs are stored and tagged with muscle names and stimulator parameters settings for later evaluation. A stand-alone TES stimulator delivers 3 biphasic pulse trains of 100 μs/phase and 1.5 ms interpulse interval. The latency times are read from a cursor and plotted along the TES-intensity scale in graphs 4A and B for the ECR and TC muscles. The courses of the latency times are similar to Fig. 3A, B. The extracranial elicited late MEPs start

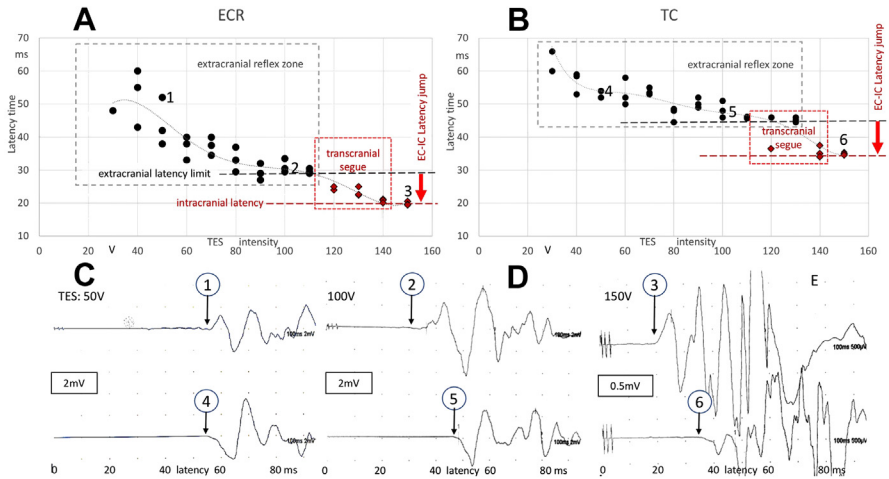

Fig. 4. Example of TES-MEP recordings of a healthy horse obtained from a standard 2-channel EMG machine modified for use in connection with a stand-alone TES voltage stimulator. The upper graphs show the course of the MEP latency times as a function of the TES intensity of the ECR (*A*) and TC (*B*) muscles on the right side. Graphs C, D, and E show the MEP traces of the ECR (upper) and the TC (lower) at TES intensities of 50, 100, and 150 V. The numbered arrows refer to the numbers in the upper plots and indicate the latency times at the onset of the responses. The measurements are performed in the Rood and Riddle horse clinic in Lexington KY and used with permission.

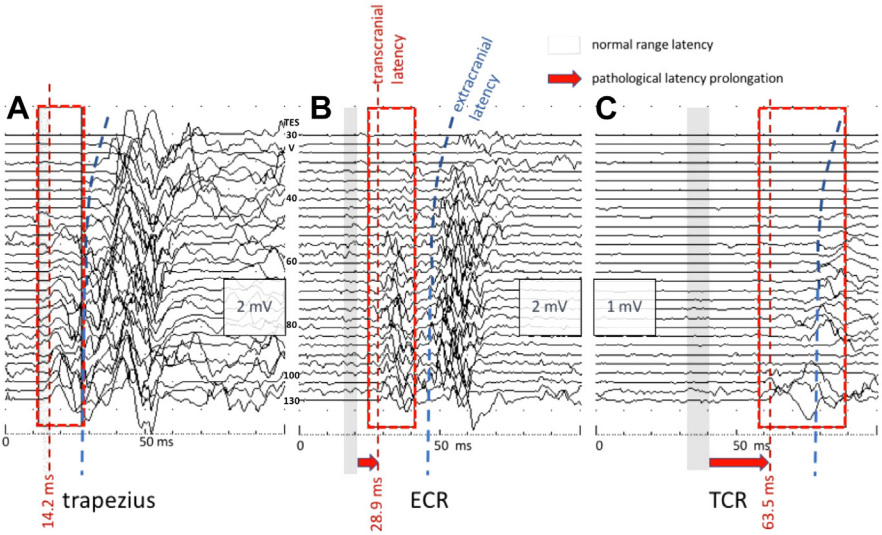

Fig. 5. Overview of TES-MEP responses from the m. trapezius (*A*), the ECR (*B*), and TC (*C*) muscle groups with from top to bottom increasing voltages. These are examples from a grade 4 ataxic horse with a spinal cord lesion. The first elicited late MEPs are of extracranial origin with relative long latency times at about 35 ms for the trapezius, 58 ms for the ECR, and strong varying latencies above 85 ms for the TC. The late latencies decrease to respectively 27 ms, 46 ms, and strong varying above 80 ms. Extra-to intracranial latencies reduction jumps are visible in all muscles between -15 and -19 ms. The gray bars represent the range of normal latencies. The red arrows indicate the prolongation of latencies from the normal. Only the trapezius latency is within the normal range.

at 30V with latencies of 50 to 60 ms for the ECR and 60 to 68 ms for the TC. These decrease to respectively 33 ms and 45 ms when reaching the transcranial threshold at 120V and 140V where extra-intra cranial latency jumps appear. Beyond the transcranial segue region, the minimum latencies and amplitudes are 19.0 ms/3.3 mV for the ECR and 35.0 ms/4.15 mV for the TC. The recorded MEPs are shown in Fig. 4C, D, E for TES voltages of 50, 100, and 150V.

The MLTs and amplitudes at the left side are 18.5 ms/13 mV and 32.0 ms/8.0 mV, respectively.

TES-MEPs of an Ataxic Horse

An example of MEPs in an ataxic horse with prolonged MLTs is illustrated in Fig. 5 whereby MEPs of the ECR and TC are shown at increasing TES voltages. The trapezius is added to illustrate the possibility of locating functional motor lesions in the cervical myelum. Like in normal horses (Fig. 3 and 4), late MEPs of extracranial origin become first visible. Their latencies reduce to 35 ms, 58 ms and strong varying latencies more than 80 ms for respectively the trapezius, ECR, and TC at the appearance of extra-to intracranial latency reductions -15 to -19 ms. The MLT of the trapezius of 14.2 ms is within the normal range, whereas the MLTs of 28.9 ms and 63.5 ms of the ECR and TC are significantly prolonged. A functional lesion is likely located between the cervical root levels C2-C4 and C6-C7 of the trapezius and ECR.

Table 1
Survey of published reference data for tc-MEP motor latencies (MLT), heights at withers

				Motor Latency Time mean ± SD (ms)		ΔMLT/Δstimint	
	Withers Height Means ± SD (cm)	N	Eloc	ECR	TCR	ECR	TCR
TMS							
Mayhew & Washbourne,[3] 1996	NA (ponies)	10	em	19.0 ± 2.3	30.2 ± 3.4		
Nollet et al,[47] 2004	137 ± 27	84	im	19.3 ± 2.5	30.5 ± 5.3	0.078	0.17
Nollet et al,[67] 2003	152 ± 5	7	im	21 ± 1.5	32 ± 3		
Nollet et al,[40] 2003	156 ± 4.5	6	im	21.1 ± 1.0	32.6 ± 2.0		
Nollet et al,[39] 2002	NA	12	im	20.7 ± 1.8	36.1 ± 3.5		
Rijckaert et al,[48] 2018	160 ± 5	10	im	20.8 ± 1.5	39.4 ± 3.8		
			em	21.2 ± 1.4	39.2 ± 3.8		
Rijckaert et al,[71] 2019	NA	5	im&em	20 ± 1	39 ± 1		
TES							
Journée et al,[42] 2018	161 ± 10	12	em	19.4 ± 0.9	36.3 ± 2.3	0.065	0.125

Survey of published reference data for tc-MEP motor latencies (MLT), heights at withers, N: number of included horses, Eloc: electrode location: extra- (em) or intramuscular (im), ΔMLT/Δstimint: MLT increase per increment of stimulation intensity (ms/% for TMS; ms/V for TES). NA: data not available.

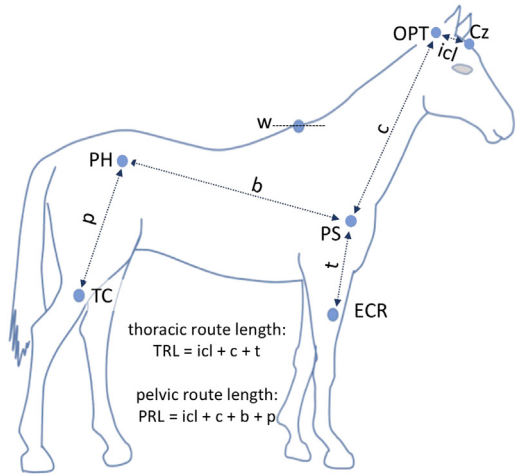

Fig. 6. Thoracic and pelvic route lengths from the vertex Cz to the ECR and TC muscles. OPT: occipital protuberance, W, height at withers; PS, point of shoulder; PH, point of hip. icl, intracranial length c, neck length; b, back length; t and p, lengths to electrodes of the thoracic and pelvic limbs. (*Modified from* Mayhew, I.G. and Washbourne, J.R. (1996) Magnetic motor evoked potentials in ponies. *J. Vet. Intern. Med.* 10, 326–9.)

INTERPRETATION OF MOTOR-EVOKED POTENTIALS

Motor Latency Times

Table 1 gives a survey of normative data of MLTs for TMS and TES of ECR and TCR muscles from the literature. Pelvic limbs show a wide latency range, which strongly depends on the length of the motor pathway between stimulation and recording. The regression coefficients ΔMLT/Δstimint expressing the MLT increase over a given increment of height at withers[47] are given in Table 1.

When comparing TES latencies with TMS, 3 and 3.8 ms should be subtracted from TMS-MEP latencies the MLTs for correction of the latency difference between TMS and TES for respectively the thoracic and pelvic limbs.

Motor Conduction Velocities

Motor conduction velocities (MCV) are expected to be independent of height as these are equal to the traveled route length divided by the MLT as described by Mayhew and colleagues.[3] The route lengths between TC stimulation and ECR or TC: TRL, and the TC: PRL, respectively are depicted in Fig. 6. These measures can be divided by the MLTs of the associated muscles for calculations of MCVs.

The velocities are compound velocities and include peripheral and central axonal motor conduction and also synaptic delays of inter- and motoneurons and neuromuscular junction. Axonal conduction velocities are therefore underestimated. MCVs of TES are higher than for TMS. This has been shown in 5 horses with heights of 160±7 cm[4] whereby for TES MCV_{ECR} = 66.2 m/s and MCV_{TC} = 73.7 m/s and for TMS: MCV_{ECR} = 58.5 m/s and MCV_{TC} = 63.8 ± 8.0 m/s.[4] The values for TMS agree with the results of Mayhew and colleagues[3] for ponies: MCV_{ECR} = 63.4 ± 9.3 m/s and MCV_{TC} = 63.8 ± 8.0 m/s, while MLTs of pelvic muscles are significant different: for

ponies: 30.2 ± 3.4 ms and taller horses: 42.6 ± 3.5 ms. This supports the expected independence of MCVs on height.

MEP Amplitudes and Morphology

Tc-MEP amplitudes are sensitive to a minor impact on the spinal cord and are a pivotal parameter in the warning criteria in neurophysiological monitoring.[22,94] In contrast to the small variability of MLTs in horses with CVs of 3% to 9%, the CVs thoracic and pelvic muscle MEP amplitudes of 35% and 60% are markedly higher with an amplitude range of 0.5 to 20 mV. Mild cervical spinal cord lesions with ataxia in the hind limbs may be visible as clearly or sometimes only slightly prolonged MLTs.[95] For statistical analysis, MEP amplitude data should be compared in the logarithmic domain whereby they have normal distribution functions.[96]

Left-right differences may have a clinical meaning.[97] Side-to-side differences of 50% or greater can be regarded as abnormal in human patients. However, Nollet and colleagues[47] reported in some normal horses, larger amplitude asymmetries. Reported MEP amplitudes of most ataxic horses are ~1 mV or smaller.[39] Cut-off values for amplitude ratios are not available. MEP amplitudes and wave shapes of extramuscular needle or surface electrodes are equal[87] but differ markedly from intramuscular needle electrodes.[48]

Pure tc-MEP amplitudes and wave shapes can only be analyzed within the transcranial time window. Published peak-peak amplitudes and phases of MEP waves likely reflect composites of transcranial and extracranial elicited MEPs. These still may have a diagnostic meaning as both MEPs result from motor conduction along the spinal cord.

CONCLUDING REMARKS

Transcranial stimulation is a valuable ancillary test to assess the integrity of the motor tracts in horses and is complementary to imaging techniques revealing the anatomy of the spine and spinal cord. TMS and TES are 2 comparable stimulation techniques whereby TES is less sensitive to modulation by cortical activity while reproducibly errors from magnetic coil repositioning are absent.

Measurements are relatively simple to perform in skilled hands. Shortest sessions with less discomfort to the horse and improved accuracy are possible with multichannel electromyographic equipment configured for equine applications. New insights in neurophysiological characteristics which apply specifically to horses' challenges to further optimize the technique and equipment by focusing on equine use and exploring the possibility to locate spinal cord lesions by identifying regions with impaired motor conduction with segmental precision. Because of its insensitivity to geometric measures of horses, it looks worthwhile to explore the features of the MCV as an alternative parameter for the motor conduction time.

CLINICS CARE POINTS

- Electrical or magnetic transcranial stimulation is painless and safe and shows good sensitivity to detect lesions along the descending motor pathways when used under sedation.
- In horses, transcranial electric and magnetic stimulation are well known as non-invasive diagnostic tests with low discomfort, under sedated conditions.
- Both techniques are able to discern between presence or absence of possible neurological lesions and identify their focal or widespread presence.

- Only thoracic and pelvic limbs muscle MEPs from TES and TMS have been documented for diagnostic evaluation in horses; except for small differences, latencies are interchangeable.
- A not skilled user may misinterpret latencies of extracranial elicited startle responses as pathological delayed transcranial MEPs.

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