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Review

Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee

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HIGHLIGHTS

- Clinical diagnostic utility of transcranial magnetic stimulation (TMS) has been established in neurological disorders.
- Paired-pulse TMS exhibits utility in neurodegenerative, movement, episodic, and functional disorders.
- TMS-EEG provides novel parameter (cortical excitability, effective connectivity, response complexity) for neurological diseases.

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A B S T R A C T

The review provides a comprehensive update (***previous report: Chen R, Cros D, Curra A, Di Lazzaro V, Lefaucheur JP, Magistris MR, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2008;119(3):504–32***) on clinical diagnostic utility of transcranial magnetic stimulation (TMS) in neurological diseases. Most TMS measures rely on stimulation of motor cortex and recording of motor evoked potentials. Paired-pulse TMS techniques, incorporating conventional amplitude-based and threshold tracking, have established clinical utility in neurodegenerative, movement, episodic (epilepsy, migraines), chronic pain and functional diseases. Cortical hyperexcitability has emerged as a diagnostic aid in amyotrophic lateral sclerosis. Single-pulse TMS measures are of utility in stroke, and myelopathy even in the absence of radiological changes. Short-latency afferent inhibition, related to central cholinergic transmission, is reduced in Alzheimer's disease. The triple stimulation technique (TST) may enhance diagnostic utility of conventional TMS measures to detect upper motor neuron involvement. The recording of motor evoked potentials can be used to perform functional mapping of the motor cortex or in preoperative assessment of eloquent brain regions before surgical resection of brain tumors. TMS exhibits utility in assessing lumbosacral/cervical nerve root function, especially in demyelinating neuropathies, and may be of utility in localizing the site of facial nerve palsies. TMS measures also have high sensitivity in detecting subclinical corticospinal lesions in multiple sclerosis. Abnormalities in central motor conduction time or TST correlate with motor impairment and disability in MS. Cerebellar stimulation may detect lesions in the cerebellum or cerebello-dentato-thalamo-motor cortical pathways. Combining TMS with electroencephalography, provides a novel method to measure parameters altered in neurological disorders, including cortical excitability, effective connectivity, and response complexity.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique for stimulating the human brain, first described in the 1980 s (Barker et al., 1985). The TMS stimulator passes a large, brief current through a coil, generating a strong time-varying electromagnetic field perpendicular to the transducing coil positioned over the scalp (Siebner et al., 2022). The magnetic field, which penetrates the scalp and skull, and is not attenuated by tissues surrounding the brain, induces an electric field in the underlying brain tissue. When stimulating the primary motor cortex (M1), the induced electric field transsynaptically activates cortical output cells (pyramidal neurons) resulting in descending corticospinal volleys, which are reflected in a motor evoked potential (MEP) (Rossini et al., 2015). Cortical TMS effects are dependent on whether a focal (figure of eight) or non-focal (circular) coils are used, pulse waveform (monophasic vs biphasic), number of pulses (e.g. paired-pulse), strength of stimulation (subthreshold vs threshold) and direction of induced cortical currents, which result in activation of distinct neuronal elements (Corp et al., 2021, Di Lazzaro et al., 2002b, Di Lazzaro et al., 1999b, Di Lazzaro et al., 2012, Di Lazzaro and Rothwell, 2014, Rossini et al., 1994, Rossini et al., 2015, Rossini et al., 2019, Siebner et al., 2022, Sommer et al., 2018).

The clinical diagnostic utility of TMS techniques have been reported across and expanding range of neurological diseases, including neurodegenerative, inflammatory, or lesional brain or spinal disorders, as well as clinical utility in investigating central pathophysiology in chronic pain, movement, episodic (epilepsy), and structural brain (stroke) disorders (Chen et al., 2008, Di Lazzaro et al., 2021, Rossi et al., 2021, Smith and Stinear, 2016, Vucic et al., 2013b). Since the last IFCN committee report (Chen et al., 2008), there have been significant advances in clinical applications of TMS in neurological diseases, leading to greater understanding of pathophysiology and development of novel diagnostic approaches. Threshold tracking TMS has emerged as a potential diagnostic technique for amyotrophic lateral sclerosis (Menon et al., 2015), while single and paired-pulse TMS (constant stimulus) techniques, as well as TMS-EEG, have yielded novel diagnostic and prognostic cortical biomarkers (Corp et al., 2021, de Goede et al., 2016, Di Lazzaro et al., 2021, Keser et al., 2022). TMS mapping of motor cortex representation based on image-guided navigated procedure of MEP recording is now an essential technique in the preoperative evaluation of brain tumor surgery to improve postoperative functional outcome. Consequently, the review will discuss advances in clinical utility of different TMS techniques, including single, paired, and triple pulse TMS, as well as TMS-EEG. The utility of repetitive TMS and other plasticity inducing techniques (such as paired-associative stimulation) will not be discussed and the reader is directed to dedicated reviews on the topic (Antal et al., 2022, Di Lazzaro et al., 2021, Gogulski et al., 2022, Harmelech et al., 2023, Lefaucheur et al., 2014, Motolese et al., 2022, Somaa et al., 2022, van den Bos et al., 2022). The first section will provide an update on specific TMS techniques, including threshold tracking TMS and TMS-EEG. The second section will discuss the application of the TMS techniques in neurological disease with an emphasis on clinical diagnostic utility.

2. TMS techniques and outcome measures

2.1. Measures of corticospinal projection

Motor threshold (MT) has been traditionally defined as the lowest TMS stimulation intensity capable of eliciting a small motor evoked potential (MEP). Rest MT (RMT) typically refers to the lowest intensity required to elicit an MEP amplitude $\geq$ 50 μV with target muscle at rest in at least 5 of 10 trials (Rossini et al., 1994, Rossini et al., 2015, Rothwell et al., 1999), while active MT (AMT) is defined as lowest intensity required to elicit an MEP amplitude $\geq$ 200 μV during slight isometric tonic muscle contraction. RMT is always higher than AMT. With the threshold tracking method, RMT is defined as stimulus intensity required to generate and maintain an MEP amplitude of 0.2 mV (±20%), a target that lies in the middle of the steepest portion of the TMS input–output (IO) curve (Fisher et al., 2002, Vucic et al., 2006). Adaptive methodology, which uses a S-shaped metric function to model the probabilistic nature of MT and the relationship between TMS intensity

and MEP amplitude (Awiszus, 2003, Rossini et al., 2015), is an alternative method of measuring MT. The mean difference between the adaptive and "constant stimulus" traditional methods was ~ 2.3% of maximal stimulator output using AMT, being higher in the former (Silbert et al., 2013).

MT indicates the excitability of a central core of neurons that represent the target muscle in the primary motor cortex (M1) and excitability of brainstem or spinal cord motor neurons. MT is lower in intrinsic hand muscles compared to proximal arm, truncal or lower limb muscles (Chen et al., 1998), reflecting difference in the strength of corticospinal projections. Voltage gated sodium channel blockers, such as phenytoin and carbamazepine, which reduce membrane excitability, increase MT (Chen R. et al., 1997, Ziemann et al., 1996a). Motor thresholds are decreased after administration of ketamine, an NMDA receptor antagonist, that simultaneously activates glutamatergic neurotransmission at AMPA and kainite non-NMDA receptors (Di Lazzaro et al., 2003). These pharmacological findings suggest that MT reflects membrane excitability of corticospinal neurons and short-lasting glutamatergic AMPA transmission. The lowest threshold for the hand motor hotspot with a figure-of-eight coil is obtained by placing the handle about 45 degrees to the sagittal line to induce posterior-anterior directed currents in the brain. For the leg motor area, the coil is placed with the handle at 90 degrees to the sagittal line with the center of coil close to Cz (Groppa et al., 2012). Motor thresholds are higher in older adults (Bashir et al., 2014), but comparable between male and females and between dominant and non-dominant limbs (Livingston et al., 2010).

2.1.1. Input-output curve, MEP amplitude, and MEP mapping

The magnetic input–output (IO) curve and MEP amplitude assess neurons that are less excitable or spatially distant from the center of target muscle representation in the M1 (Chen, 2000, Hallett et al., 1999). The gradient of the sigmoidal IO curve is determined by the degree of activation of corticospinal neurons as well as the strength of corticospinal projections onto the target muscle. Muscles with lower MT, such as intrinsic hand muscles, exhibit steeper IO curves (Chen et al., 1998), as do younger adults with no gender effects (Pitcher et al., 2003). IO curve gradients are steeper in the non-dominant compared to the dominant hemisphere (Daligadu et al., 2013), suggesting that the non-dominant hemisphere may have a higher level of excitation or a lower level of inhibition. The slope of the IO curve is increased by drugs that increase adrenergic transmission and decreased by sodium and calcium channel blockers as well as agents that enhance GABAergic effects (Ziemann et al., 2015). It should be stressed that the MEP amplitude is significantly smaller than the maximal compound muscle action potential amplitude (Rosler et al., 2002). This is related to desynchronization of descending corticospinal volleys resulting in phase cancellation and asynchronous recruitment of spinal or bulbar motor neurons.

Marked trial-to-trial variability of MEP amplitude with constant TMS intensity is a well-known phenomenon (Kiers et al., 1993). The physiological mechanisms underlying MEP variability include: (i) fluctuation of neuronal excitability at cortical and spinal cord levels (Rossini et al., 2015), (ii) timing of TMS stimulus application in relation to the peaks or troughs of specific cortical oscillatory states (Metsomaa et al., 2021), and (iii) activation of target muscle (Darling et al., 2006). Specifically, TMS delivered during the trough and rising phase of the μ rhythm generates larger MEPs, while TMS at peak and the falling phase of μ rhythm elicits smaller MEPs (Wischnewski et al., 2022, Zrenner et al., 2018). MEP variability may be reduced, and amplitude increased when TMS is triggered at the optimal phase of individualized β oscillation (Torrecillos et al., 2020). The MEP variability prompted the development of the threshold tracking technique which relies on TMS intensity rather than MEP amplitude as an outcome measure (Vucic et al., 2006).

TMS mapping can be used for probing cortical motor representation and enabling delineation of somatotopy of different muscle groups. Although different mapping protocols have been utilized, these are often used to locate the center of gravity (COG) (Wassermann et al., 1992). The most basic method includes applying a 1 cm grid on the scalp and stimulating each point on the grid with TMS intensity at 110 ~ 120% RMT [landmark-guided mapping] (Sondergaard et al., 2021a). The mapping procedure starts from the selected muscle motor hotspot and moves in either anterior-posterior or medial–lateral direction at each marking on the grid until no MEP can be obtained, indicating the edge of the map. The coil is subsequently moved to identify borders of the map. Usually, 10–20 trials per site are recorded (Classen et al., 1998). Although more sampling trials per site provide more precise COG measurement, it is more time consuming (Classen et al., 1998). The COG is calculated from the amplitude weighted average of the MEP amplitude at each stimulation site, or the MEP amplitude at a site can be presented as the ratio to the averaged MEP size of the whole mapping area (Ngomo et al., 2012).

At present, conventional cortical mapping methods based on anatomical landmarks are outdated, due to the development of image-guided navigation tools. Navigation is based on a frameless stereotaxic system dedicated to TMS, co-registration of the coil positioning on the scalp and individual brain imaging (MRI or fMRI) of the subject (Lefaucheur, 2010) This is the best way to ensure the accuracy of coil placement and the reliability and repeatability of cortical mapping with reduced variability between sessions (Gugino et al., 2001). Navigation systems have the advantage of providing real-time feedback and demonstrate the location of the sites of cortical stimulation producing MEPs relative to classical anatomical structures, such as the motor hand knob, central sulcus or other gyral features (Jonker et al., 2019). Presurgical navigated TMS mapping procedures are now largely used in clinical practice to delineate eloquent cortical regions and preserve motor or language functions from deleterious lesions secondary to brain tumor resection or epilepsy surgery (Lefaucheur and Picht, 2016). Robotic-assisted TMS may lead to further improve coil handling and mapping procedure accuracy in combination with navigation (Ginhoux et al., 2013, Harquel et al., 2016).

2.1.2. Central motor conduction time

Central motor conduction time (CMCT) includes the excitation time of motor cortical neurons, conduction via the corticospinal tract and time to excite spinal motor neurons to threshold. CMCT is measured as the difference between MEP latency and spinal motor neuron latency to the target muscle, known as the peripheral motor conduction time (PMCT). The PMCT can be estimated using the F-wave method as reflected by the following formula **(F + M−1)/2**, where F represents the shortest F-wave latency, M is the distal motor latency and 1 ms represents the turnaround time for spinal motor neurons activated antidromically (Mills, 1999). It has also been suggested that the longest F-wave latency may be used (Olivier et al., 2002). Alternatively, PMCT may be estimated by subtracting the MEP or compounding muscle action potential onset latencies, induced by magnetic or electrical stimulation respectively over the vertebral columns, from the cortical MEP latency (Mills and Murray, 1986). The latter method excites the spinal nerves at the spinal foramen and has the advantage of being recordable form most muscle. As for the latter method, CMCT may be overestimated, especially when recoding from lower limb muscles, since the conduction time in proximal nerve root segment between spinal cord and exit foramen is included. To overcome this overestimation, we should use cortico-conus conduction time (CCCT) for leg muscles (Matsumoto et al., 2010a).

To obtain the shortest CMCT, the target muscle should be activated at ~ 10% to 20% of maximum background force (Mills, 1999). The active MEP latency is 1.5-to-2.5 ms shorter than rest MEP latency (Mano et al., 1992), termed "latency jump", and is more prominent in children (Caramia et al., 1993). It is recommended to superimpose at least five responses and measure the shortest latency. Contraction of homologous contralateral muscles is an option for patients unable to produce adequate target muscle contraction (Mariorenzi et al., 1991).

Age is weakly correlated with CMCT in adults (Claus, 1990, Mano et al., 1992, Matsumoto et al., 2012, Mills and Nithi, 1997b). Immaturity of the corticospinal system, as in preterm and term babies, results in longer CMCT (Eyre, 2007). When measured from the lower limbs, CMCT correlates with height, although this correlation is not evident in upper limb CMCT (Matsumoto et al., 2012, Rossini et al., 1987, Wochnik-Dyjas et al., 1997). Additionally, upper limb CMCT is not influenced by gender or hand dominance, and there are no significant side-to-side differences (Livingston et al., 2010, Toleikis et al., 1991). In contrast, lower limb CMCT is marginally shorter in women, even allowing for differences in height (Toleikis et al., 1991).

2.1.3. Cortical silent period

The cortical silent period (CSP) refers to electrical silence of background electromyography (EMG) activity in a contracting muscle following suprathreshold TMS of M1 and varies from 50-to-300 ms (Cantello et al., 1992). The CSP duration increases with stimulation intensity, but is not related to size of the preceding MEP response (Triggs et al., 1992) or strength of target muscle contraction (Inghilleri et al., 1993, Kimiskidis et al., 2005). Low levels of muscle contraction are suggested to avoid muscle fatigue that may inadvertently prolong the CSP duration (Hunter et al., 2006). The CSP duration is longer with anterior-to-posterior compared to posterior-to-anterior directed currents (Orth and Rothwell, 2004). Moreover, the CSP can be elicited with subthreshold TMS intensity without a preceding MEP (Trompetto et al., 2001), suggesting that CSP is not directly related to MEP generation.

The CSP can be recorded in different muscles such as lower limb (Ziemann et al., 1993), facial (Werhahn et al., 1995), diaphragm (Lefaucheur and Lofaso, 2002) and sphincter muscles (Lefaucheur, 2005), although the duration is longest when recorded from intrinsic hand muscles. The first 50 ms of CSP involves spinal inhibitory circuits (Fuhr et al., 1991, Pierrot-Deseilligny and Burke, 2012, Rossini et al., 2015), while the later parts of the CSP are of cortical origin mediated by GABAergic neurotransmission acting via $GABA_B$ receptors (Classen and Benecke, 1995, Stetkarova and Kofler, 2013). The non-dominant hand exhibits longer CSP duration than the dominant hand, suggesting that circuits underlying CSP generation are less excitable in the dominant hemisphere (Priori et al., 1999). Although most of studies revealed reduced CSP in older adults (Davidson and Tremblay, 2013, Oliviero et al., 2006, Sale and Semmler, 2005), some studies reported a comparable CSP duration between young or older adults (Fujiyama et al., 2012, Hunter et al., 2008). CSP duration is not affected by gender (Shibuya et al., 2016a).

Ipsilateral inhibition (ipsilateral silent period, iSP) induced by motor cortex stimulation can be measured by interruption of ongoing voluntary EMG activity in muscles ipsilateral to cortical TMS (Chen et al., 2008). The iSP reflects transcallosal inhibition (Meyer et al., 1995), although non-callosal pathways caudal to the corpus callosum may also contribute (Compta et al., 2006). The iSP usually begins 30 ~ 40 ms after a TMS and lasts for 20-to-25 ms (Meyer et al., 1995). Although iSP duration could be a simple measure of the iSP response, the recommended measurement is to normalize the area of the rectified trace between onset and offset of the iSP to the pre-stimulus mean baseline EMG level (Kuo et al., 2017). To attain the largest iSP response, at least 60% of maximal TMS output may be required (Meyer et al., 1995). To avoid muscle fatigue, its recommend that participants either sustain a low-level contraction (15–20% maximum voluntary contraction) for the entire duration of the trial, or perform short, near-maximal contraction bursts with standard inter-trial rest intervals between each subsequent stimuli (Hupfeld et al., 2020). The latter option may function better in older populations who are more susceptible to muscle fatigue. The iSP onset, end latency and transcallosal time, as well as area, is increased in older adults (Davidson and Tremblay, 2013, Petitjean and Ko, 2013), suggesting that transcallosal inhibition declines with age. In contrast, the extent of muscle contraction, direction of TMS induced current, or limb dominance do not appreciably affect the iSP (Chen et al., 2003, Davidson and Tremblay, 2013, Hunter et al., 2006, Kuo et al., 2017).

2.2. Measures of cortical inhibition and facilitation

2.2.1. Short interval intracortical inhibition

SICI was first described in 1993 and is the most frequently used paired-pulse TMS paradigm to evaluate motor cortex excitability (Kujirai et al., 1993). Primary motor cortex (M1) stimulation with a subthreshold conditioning stimulus (CS) followed by suprathreshold test stimulus (TS) at inter-stimulus intervals (ISI) of 1-to-6 ms decreases MEP amplitude compared to TS alone, termed the "***constant stimulus***" method (Kujirai et al., 1993). Subsequently, ***a threshold tracking paired-pulse TMS technique*** was developed, whereby a fixed MEP amplitude (0.2 mV ± 20%) was tracked by a test stimulus (TS), with ISIs increased in a sequential ascending order (Vucic et al., 2006). SICI is heralded by a greater conditioned-test stimulus intensity required to generate and maintain a target MEP response, developing between ISIs of 1-to-7 ms [Fig. 1] (Awiszus et al., 1999, Fisher et al., 2002, Vucic et al., 2006). Two maximum phases of inhibition have been described, occurring at ISIs of about 1 and 2.5-to-3 ms (Fisher et al., 2002, Hanajima et al., 2003, Roshan et al., 2003, Vucic et al., 2006). The inter-session reliability and reproducibility of mean SICI (between ISIs 1-to-7 ms), as reflected by a low intraclass correlation coefficient (ICC), was established (Matamala et al., 2018), suggesting a potential clinical diagnostic utility. Recently, a threshold tracking TMS paradigm was developed with ISIs delivered in a pseudo-random fashion, with 10 stimuli at each ISI level (Tankisi et al., 2021), and was shown to exhibit comparable reliability and reproducibility as the "constant stimulus" method (Nielsen et al., 2021).

A cortical origin of SICI was suggested by epidural recordings, whereby the subthreshold CS suppressed recruitment of late I waves (especially I_3 waves) elicited by the TS (Di Lazzaro and Rothwell, 2014). Pharmacological studies have suggested that inhibitory interneuronal circuits acting, via $GABA_A$ receptors, mediate the second phase of SICI at ISIs 2.5-to-3 ms (Di Lazzaro et al., 2007a, Ziemann et al., 1996a, Ziemann et al., 2015). Increased axonal refractoriness or synaptic mechanisms have been proposed as underlying physiological mechanisms mediating SICI at ISI 1 ms (Chen, 2004, Fisher et al., 2002, Hanajima et al., 2003, Vucic et al., 2011a, Vucic et al., 2009), as well as shunting inhibition by opening channels in proximal dendrites targeted by incoming afferents (Paulus and Rothwell, 2016).

SICI is a general inhibitory effect which is evident in different muscles, including proximal arm (Abbruzzese et al., 1999), facial (Paradiso et al., 2005), lower limb (Chen et al., 1998, Menon et al., 2018) muscles, as well as the trapezius (Menon et al., 2018), diaphragm (Demoule et al., 2003) and sphincter muscles (Lefaucheur, 2005). While SICI appears not be to be influenced by handedness or hemispheric laterality (Cahn et al., 2003, Dharmadasa et al., 2019, Menon et al., 2019), some have reported a reduction of SICI in the dominant hemisphere in right handed

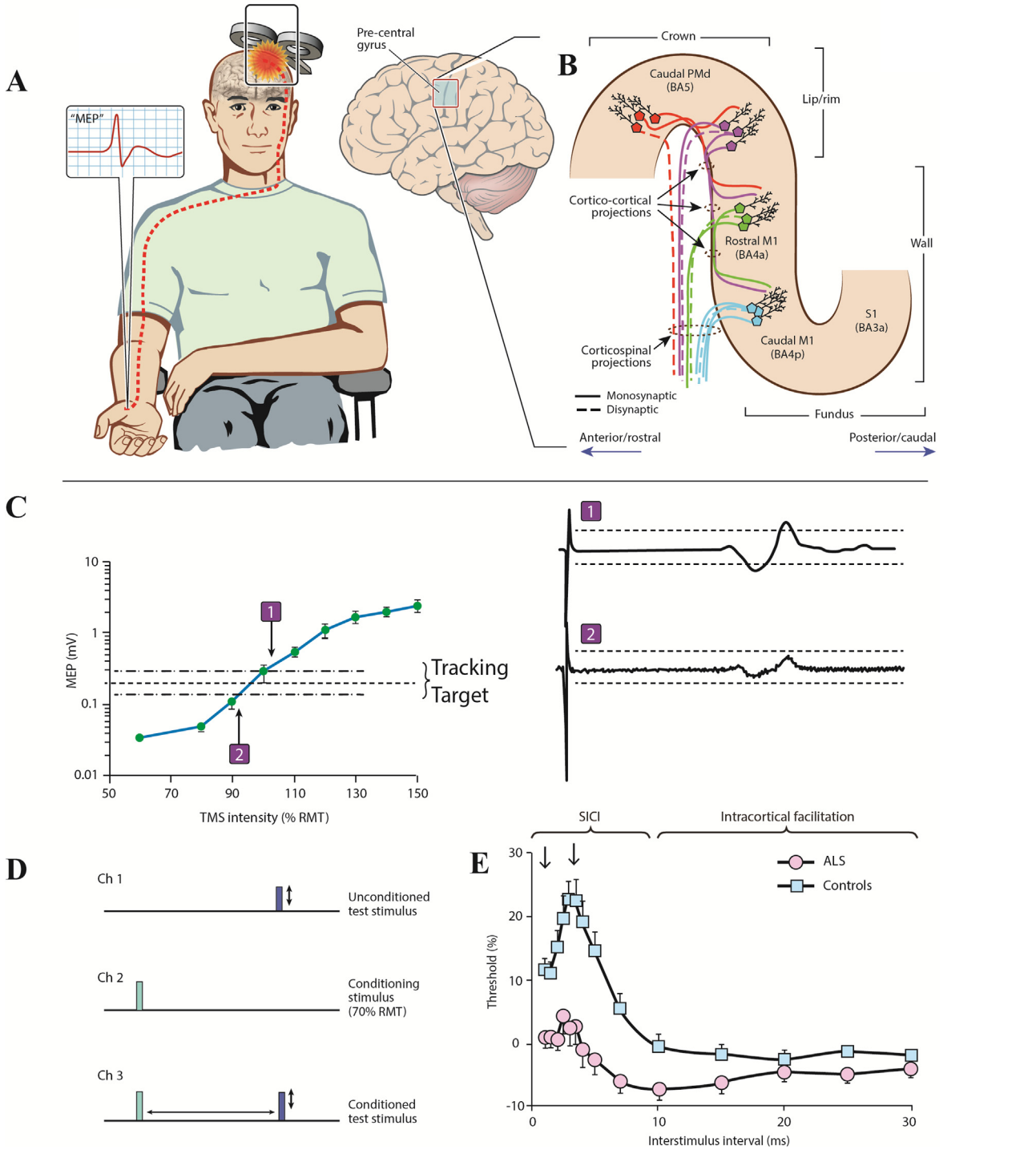

Fig. 1. Principles of single and paired-pulse TMS. (A) Transcranial magnetic stimulation using a figure of eight coil and applied over the primary motor cortex (M1), elicits a motor evoked potential (MEP, red potential in inset) from a target muscle. **(B)** Candidate descending corticomotoneuronal pathways from the precentral gyrus that contribute to the MEP response. Direct neuronal activation most likely occurs in the lip/rim regions of the motor hand knob. Activation spreads to the rostral and caudal parts of the M1, via cortico-cortical synaptic transmission, potentially contributing to indirect waves; (I-waves). There is a greater preponderance of fast-conducting monosynaptic cortico-motoneuronal neurons in the caudal M1 (BA4p) compared to the rostral M1 (BA4a) is highlighted. The exact transition between rostral M1 and caudal dorsal premotor cortex (PMd) in the lip/rim region of the gyrus is gradual and varies across subjects. Additional corticospinal pathways may be activated by TMS via excitation of postcentral primary somatosensory cortex (S1) and its cortico-cortical projections to rostral/caudal M1. **(C)** For threshold tracking TMS, a target of 0.2 mV (±20%) is selected which lies in the steepest portion of the stimulus response curve. As such, if the MEP response is larger than the tracking target (potential-1) the subsequent stimulus intensity is reduced, while if the MEP response is smaller than the tracking target (potential-2), the subsequent stimulus intensity is reduced. **(D)** The paired pulse paradigm is illustrated. Channel 1 records an unconditioned test stimulus, defined as TMS intensity required to generate and maintain the tracking target, which signifies the resting motor threshold (RMT) when using the threshold tracking technique. Channel 2 monitors the subthreshold conditioning stimulus (does not generate MEP) and channel 3 records the conditioned-test stimulus at interstimulus intervals of 1–30 ms. **(E)** When utilizing the threshold tracking TMS technique, short interval intracortical inhibition (SICI) is represented as increased conditioned-test stimulus intensity required to generate and maintain the tracking target, developed between 1–7 ms. Intracortical facilitation is represented as reduced conditioned-test stimulus intensity. In amyotrophic lateral sclerosis (ALS) patients SICI is reduced and ICF increased, signifying cortical hyperexcitability.

subjects (Hammond et al., 2004, Ilic et al., 2004). Given that a recent study suggested that brain derived neurotrophic factor (BDNF) polymorphism might influence interhemispheric balance of SICI, the discrepancies across different studies may be explained by variations of BDNF polymorphism in the studied populations (Dubbioso et al., 2022b). Additionally, male and female subjects exhibit comparable SICI values (Cahn et al., 2003, Hermsen et al., 2016).

SICI critically depends on the CS and TS intensities, being absent when the TS intensity is < 110% RMT (Garry and Thomson, 2009) and increases with higher TS intensities (Daskalakis et al., 2004, Roshan et al., 2003, Sanger et al., 2001). At low CS intensities, SICI is reduced or absent and increases as the CS intensity is increased, but then diminishes at even higher CS intensities and becoming facilitatory when CS is close to RMT, resulting in a U-shaped curve response (Chen et al., 1998, Peurala et al., 2008, Vucic et al., 2009). SICI may be reduced immediately after contraction of target muscle and is influenced by coil type (Dharmadasa et al., 2019, Menon et al., 2018, Van den Bos et al., 2018, Vucic et al., 2011a). Preferential recruitment of interneuronal circuits generating I3 waves was correlated with higher SICI values (Hanajima et al., 1998, Higashihara et al., 2020). At a physiological level, SICI may serve to focus output from motor cortex to enable selective activation of specific muscles and prevent unwanted activation of other muscles (Rosenkranz and Rothwell, 2004, Stinear and Byblow, 2003, Zoghi et al., 2003).

2.2.2. Intracortical facilitation

Intracortical facilitation (ICF) is elicited with a similar paradigm as SICI, except the ISI is between 8–30 ms, with the most prominent facilitation evident from 10-15 ms (Kujirai et al., 1993, Vucic et al., 2006). ICF is not a rebound disinhibition of SICI as its threshold is slightly higher (Chen et al., 1998, Ziemann et al., 1996b). Since ICF can be produced by subthreshold CS that does not evoke descending corticospinal volleys, ICF likely occurs at a cortical level. Epidural spinal recordings did not show changes in amplitude or number of D-wave or I-waves with ICF (Di Lazzaro et al., 2006b), suggesting that ICF may be either mediated by cortical circuits other than those generating I-waves, or yet to be discovered physiological mechanisms operating at a spinal level (Chen et al., 2008, Di Lazzaro and Rothwell, 2014). Administration of NMDA receptor antagonist dextromethorphan reduced ICF (Ziemann et al., 1998a), while chronic administration of the serotonin re-uptake inhibitor paroxetine enhanced ICF (Gerdelat-Mas et al., 2005), suggesting the involvement of glutamatergic and serotonergic neurotransmission in generating ICF. Sodium channel blockers, age and gender did not appreciably impact ICF (Bhandari et al., 2016, Chen R. et al., 1997, Shibuya et al., 2016a). While one study reported greater ICF in the dominant hemisphere (Civardi et al., 2000), others have not reported hemispheric asymmetry (Lefaucheur et al., 2008).

2.2.3. Short interval intracortical facilitation

Short interval intracortical facilitation (SICF) is recorded by using a paired-pulse paradigm whereby a suprathreshold first stimulus (S1) and subthreshold or threshold second stimulus (S2) is delivered at short ISIs leading to an increase in the conditioning-test MEP amplitude (Chen and Garg, 2000, Ziemann et al., 1998b). Alternatively, both S1 and S2 stimuli may be set to motor thresholds also resulting in conditioning-test MEP facilitation (Tokimura et al., 1996). Using this constant stimulus method, three SICF facilitation peaks have been identified at discrete ISIs: 1.1–1.5, 2.3–3.0, and 4.1–4.5 ms (labeled as SICF-1, SICF-2 and SICF-3). Recently, a threshold tracking paradigm was developed whereby S1 and S2 were set to threshold, and SICF was reflected by reduction in test stimulus intensity required to generate and maintain a target MEP response of 0.2 mV (±20%) (Van den Bos et al., 2018). As with the constant stimulus method, SICF developed between ISIs of 1–5 ms, with two peaks evident at ISI 1.5 and 3 ms. Voluntary target muscle contraction, handedness and age do not affect SICF (Bäumer et al., 2007, Chen et al., 2008, Ilic et al., 2004, Van den Bos et al., 2018), although assessment with a figure-of-eight coil compared to circular coil and lower tracking targets (0.2 vs 1.0 mV) increase SICF (Van den Bos et al., 2018).

The precise physiological mechanisms mediating SICF remain to be fully elucidated.

It has been proposed that facilitatory interactions of I-waves at a motor cortical level form the basis of SICF (Ziemann et al., 2015, Ziemann et al., 1998c). TMS modelling studies of induced I-waves suggested that the suprathreshold S1 stimulus leads to subliminal depolarization of a subpopulation of cortical neurons (Rusu et al., 2014). A subsequent subthreshold stimulus (S2) applied at short ISIs causes the subliminally depolarized neurons to reach threshold, thereby generating an MEP potential and resulting in facilitation (Hanajima et al., 2002). Support for a cortical origin was suggested by the observed periodicity of SICF peaks, which occur at 1.5 ms (~660 Hz), being consistent with I-wave frequency (Amassian et al., 1987). Pharmaco-TMS studies have provided additional support for a cortical origin, documenting a modulating effect on SICF by a variety of neurotransmitter systems (Ilic et al., 2003, Ilic et al., 2002, Korchounov and Ziemann, 2011, Ziemann et al., 2015), all of which are involved in the neuronal circuitry underlying I-wave generation (Di Lazzaro and Ziemann, 2013). The facilitating effects of SICI on SICF (Wagle-Shukla et al., 2009) provided additional evidence for importance of cortical neuronal circuitry in SICF via disynaptic inhibition. TMS intensities and paired-pulse intervals for SICF overlap with SICI, and recruitment of SICF may explain the reduction of SICI at high CS intensities (Ni et al., 2013, Peurala et al., 2008). Therefore, it has been suggested the CS intensity for SICI be kept below AMT and the ISI occur at the trough of SICF to minimize the influence of SICF on SICI (Rossini et al., 2015).

2.2.4. Long interval intracortical inhibition

Long-interval intracortical inhibition (LICI) is typically elicited by a suprathreshold CS followed by a suprathreshold TS at ISI from 50 to 200 ms (Valls-Sole et al., 1992, Vucic et al., 2006, Wassermann et al., 1996). Evidence that LICI occurs at a cortical level includes; (i) finding of no change in spinal excitability at more than 50 ms after suprathreshold TMS (Fuhr et al., 1991), (ii) absence of LICI with paired transcranial electrical stimulation (Inghilleri et al., 1993), and (iii) epidural recordings disclosing marked reduction of descending corticospinal test volleys (Chen et al., 1999b, Di Lazzaro et al., 2002a, Nakamura et al., 1997). With reduction of CS intensity to subthreshold levels, facilitation may be observed (Chen et al., 1998, Vallence et al., 2014). LICI appears to be mediated by $GABA_B$ post-synaptic receptors (McDonnell et al., 2006) and may be enhanced by $GABA_B$ receptor agonists (baclofen), GABA analogs (vigabatrin) and GABA uptake inhibitor (tiagabine) (McDonnell et al., 2006, Pierantozzi et al., 2004a, Ziemann et al., 2015). There is evidence that LICI at ISI 100 ms is more prominent in the dominant hemisphere in younger adults (Hammond and Garvey, 2006) and this asymmetry decreases with age (Vallence et al., 2017). LICI is reduced with increasing TS intensity (Sanger et al., 2001) and is not substantially affected by target muscle contraction (Chen R. et al., 1997). Late cortical disinhibition following LICI has been described, which represent a period of late facilitation after LICI (Cash et al., 2010, Caux-Dedeystère et al., 2014). Using a triple pulse stimulation paradigm, LICI inhibits SICI, likely through the pre-synaptic $GABA_B$ receptor mediated inhibition (Ni et al., 2011).

2.2.5. Interhemispheric inhibition and interhemispheric facilitation

Interhemispheric inhibition (IHI) is typically recorded by delivering a suprathreshold CS to M1 in one hemisphere followed by a suprathreshold TS to the opposite M1 (Ferbert et al., 1992, van den Bos et al., 2021). Two types of IHI have been described: short-latency IHI (SIHI) between ISI 6-to-11 ms (maximum at ISI ~ 9.6 ms), and long-latency IHI (LIHI) between ISIs 20-to-50 ms (Chen et al., 2003, Ni et al., 2020). SIHI and LIHI are more prominent in distal than proximal muscles (Perez and Cohen, 2009, Rossini et al., 2015). Higher CS intensities elicit IHIs at longer ISIs [> 50 ms] (Ferbert et al., 1992). Cervical epidural recordings showed that IHI occurs at a cortical level since it was associated with reduction of later I-waves (particularly I_3) (Di Lazzaro et al., 1999c). At a physiological level, CS exerts an inhibitory effect via activation of excitatory transcallosal fibers that activate GABAergic inhibitory circuits in the opposite motor cortex and thereby lead to inhibition of the MEP response evoked by a TS (Irlbacher et al., 2007, Reis et al., 2008).

SIHI can be elicited from the premotor cortex with subthreshold test stimuli that are medially directed (Mochizuki et al., 2004) or suprathreshold test stimuli with anteriorly directed currents (Bäumer et al., 2007). LIHI can be elicited by conditioning stimulation of the contralateral somatosensory cortex (Iwata et al., 2016, Ni et al., 2009). Handedness or hemispherical dominance may affect IHI, with stronger inhibition when the conditioning stimulation is applied over the dominant hemisphere (Bäumer et al., 2007, Netz et al., 1995). This, however, is not a universal finding (De Gennaro et al., 2004), and could be related to use of different stimulation coils and induced current directions.

Interhemispheric facilitation (IHF) may be elicited by applying the CS over the M1 (at ISIs 3-to-6 ms) or premotor cortex (ISIs 6-to-8 ms) ipsilateral to the target muscle, followed by a TS delivered to the contralateral M1 (Bäumer et al., 2006, Hanajima et al., 2001). IHF can be elicited either during active muscle contraction or at rest, with CS set to subthreshold (target muscle at rest) or suprathreshold (target muscle is active) (Bäumer et al., 2006, Hanajima et al., 2001) intensities. The magnitude and latency distribution of IHF correlates with IHI (Ni et al., 2020). Magnetic (lateral-medial direction) and anodal electrical stimulation may generate IHF, suggesting that activation of corticospinal neurons and subsequent transmission through the corpus callosum is a likely mechanism (Hanajima et al., 2001). The facilitatory effects are also related to I_3 wave recruitment, suggesting a role for interneuronal circuits (Hanajima et al., 2001). Long-latency IHF (at ISIs > 80 ms) has also been reported with suprathreshold CS delivered to M1 or subthreshold CS to dorsal premotor cortex or supplementary motor area (Fiori et al., 2017).

2.2.6. Short latency afferent inhibition

Afferent input from cutaneous or mixed nerves innervating the hand may decrease cortical excitability if delivered prior to TMS applied over the contralateral motor cortex, termed short-latency afferent inhibition (SAI). MEP amplitude is reduced when electrical stimulation of the median nerve at the wrist is delivered 18-to-28 ms before a TMS stimulus (Ni et al., 2011, Tokimura et al., 2000). The ISI is slightly longer for digital cutaneous nerve stimulation to account for conduction time from the digit to wrist. For example, MEP amplitude of intrinsic hand muscles is reduced when preceded by digital nerve stimulation of the index finger 20–50 ms before TMS (Tamburin et al., 2005). SAI in the abductor digit minimi muscle can be elicited when stimulation from the 5th digit preceded TMS by 20 to 45 ms (Tamburin et al., 2001). Mixed nerve stimulation activates muscle afferents, joint and cutaneous mechanoreceptors, whereas digital stimulation only activated cutaneous fibers (Turco et al., 2018b).

Maximum SAI occurs at ISIs of ~ N20 latency plus 2 ms, or ~ 20–22 ms for median nerve stimulation at wrist and ~ 25 ms for digit stimulation (Bikmullina et al., 2009, Rossini et al., 2015). SAI reaches maximal level at a stimulating intensity that recruits all the sensory afferents as reflected by the sensory nerve action potential amplitude (*3 times the sensory perception threshold for digital nerve stimulation, or 1.2 times motor threshold for mixed nerve stimulation*) (Bailey et al., 2016, Turco et al., 2018b). SAI is mediated by cortical mechanisms since epidural recordings disclosed suppression of I_2 and I_3 waves (Tokimura et al., 1996), and appears unrelated to alterations in spinal cord excitability (Delwaide and Olivier, 1990). Importantly, anterior-posterior directed currents leads to less SAI than posterior-anterior directed TS (Ni et al., 2010), suggesting that specific interneuronal circuits generating later I-waves exhibit different sensitivity to SAI. Mixed nerve SAI is reduced during movement or just before movement begins (Asmussen et al., 2013), indicating a modulating effect of motor cortex on afferent inputs. Additionally, SAI is enhanced by cholinergic transmission (Di Lazzaro et al., 2005, Di Lazzaro et al., 2000, Fujiki et al., 2006) and reduced by GABAergic transmission (Di Lazzaro et al., 2007a, Teo et al., 2009). Higher test MEP amplitude is associated with lower SAI (Ni et al., 2011), although this is not a universal finding (Toepp et al., 2021). Intersession test–retest reliability is high, and SAI is not affected by age, gender, or time of day. However, some normal subjects still showed fluctuation between inhibitory and facilitatory responses (Toepp et al., 2021).

2.2.7. Long latency afferent inhibition

When a peripheral nerve afferent stimulation is applied ~ 200 ms before a contralateral TMS to the motor cortex, the MEP amplitude is reduced and is termed long-latency afferent inhibition (LAI) (Chen et al., 1999a). Peripheral nerve stimulation may be from a mixed or pure sensory nerve. The response is typically recorded form an intrinsic hand muscle. With cutaneous nerve stimulation (typically digit 3), the ISI range of LAI is ~ 200 to 600 ms when recording from the abductor pollicis brevis (Chen et al., 1999a). Mixed and cutaneous nerve stimulations lead to LAIs of similar magnitude (Abbruzzese et al., 2001, Turco et al., 2017). The stimulation intensity required to achieve maximal LAI magnitude is ~ 50% of maximum sensory nerve action potential amplitude, representing an intensity of two times sensory perception threshold for digital nerves or motor threshold for mixed nerves. Given the long interval between peripheral stimulation and a subsequent TMS pulse, the afferent input may be relayed through the basal ganglia-thalamocortical loop to the contralateral primary somatosensory cortex, posterior parietal cortex and secondary somatosensory cortex before arriving at the motor cortex (Allison et al., 1989, Kawamura et al., 1996, Sailer et al., 2003, Turco et al., 2017). There is evidence that LAI is modulated by $GABA_A$ receptor mediated circuits (Turco et al., 2018a). Similar to SAI, age and gender does not affect LAI (Toepp et al., 2021).

2.2.8. Cerebellar inhibition

The modulatory effects of cerebellar stimulation on the contralateral motor, termed cerebellum-to-motor cortex inhibition (CBI), was first studied by high-voltage electrical stimulation (Groiss and Ugawa, 2013, Ugawa et al., 1991a) and later by double cone magnetic stimulation (Fernandez et al., 2018a, Mooney et al., 2022, Rurak et al., 2022, Spampinato et al., 2020, Ugawa et al., 1995b). Magnetic cerebellar stimulation is most reliably elicited by using a double cone coil, positioned over the midpoint on a line between inion and external auditory meatus (Ugawa et al., 1995b, Werhahn et al., 1996) or 3–5 cm lateral and 0 or 2 cm above the inion (Fernandez et al., 2018a), with upward induced current in the cerebellar cortex (Reis et al., 2008). The cerebellar

conditioning stimulation intensity is set at 5–10% below AMT for foramen magnum double cone stimulation (Ugawa et al., 1995b, Werhahn et al., 1996). To activate cerebellar Purkinje cells, the intensity of cerebellar CS is usually high and may cause discomfort. The double cone coil provides the most consistent CBI results, with no further increase in inhibition when CS intensity exceeds 60% of maximum stimulator output [MSO] (Fernandez et al., 2018b). Figure-of-eight coils do not elicit an adequate and consistent CBI response, and therefore are not recommended (Fernandez et al., 2018b, Ugawa et al., 1995b, Werhahn et al., 1996). Suppression is not observed with electrical test stimulation applied to the primary motor cortex, suggesting that interactions occur at the cortical level.

Cerebellar stimulation suppresses the MEP response at ISIs of 5–8 ms mediated by cerebellar activation and spinal inhibitory processes (ISI 7–8 ms) (Fernandez et al., 2018a, Werhahn et al., 1996). Underscoring the importance of cerebellar activation are findings that CBI was absent in patients with cerebellar degeneration (Ugawa et al., 1997). Activation of Purkinje cells, located in the cerebellar posterior lobules V-VIII and ~ 30 mm below the scalp, mediate development of CBI (Hardwick et al., 2014). Purkinje cell activation reduces the tonic facilitatory drive from dentate nucleus to contralateral M1 through the dentate-thalamo-cortical pathways (Pinto A. D. and Chen R., 2001, Ugawa et al., 1997). Cerebellar inhibition is more prominent with smaller (~0.5 mV) than larger test MEP amplitudes (~2 mV), a finding related to either predominant I_1 wave modulation, or projection of dentate-thalamo-cortical fibers to the core of cortical hand muscle representation area (Pinto Andrew D and Chen Robert, 2001, Reis et al., 2008). Cerebellar inhibition may modulate premotor cortex excitability with maximal inhibition at ISI of 7 ms when the TS induced currents are directed anterior-posteriorly in the motor cortex (Spampinato et al., 2020).

It should be stressed that two independent cerebello-M1 pathways may contribute to CBI (Spampinato et al., 2020). Specifically, one cerebello-M1 pathway (assessed by posterior-anterior directed currents) targets excitability of M1 layer 5 pyramidal neurons in the rostral lip, while the other pathway (activated by anterior-posterior directed currents) targets excitability of neurons in the premotor cortex that project onto M1. Assessment of these pathways should be considered in pathophysiological studies. Of relevance, CBI may reduce SICI and increase ICF, suggesting an effect on inhibitory and facilitatory cortical circuits (Daskalakis et al., 2004). Factors such as age influence CBI, with the magnitude of cerebellar inhibition being smaller in older adults, a finding potentially mediated by an age-related loss of Purkinje cells (Rurak et al., 2022). Others have reported the converse and argued that the increase in CBI in older adults was a compensatory mechanism to support age-related motor function decline (Mooney et al., 2022). The discordant findings may be related to use of different coil types with figure-of-eight coil used by the former (Rurak et al., 2022) and double-cone coil in latter study (Mooney et al., 2022). At a physiological level, the pathways assessed by CBI seem to be important for gait performance, whereby greater CBI is associated with a faster 10-meter walking time (Rurak et al., 2022). This finding was attributed to importance of rhythmic upper limb movement in gait control (Ortega et al., 2008).

Inadvertent stimulation of CSTs by the CS may confound CBI by three potential mechanisms: (i) collision of antidromic CST with descending M1 volleys; (ii) activation of CST collaterals which activate cortical inhibitory neurons; and (iii) depolarization of spinal motor neurons by descending CST volleys (Fisher et al., 2009, Ugawa et al., 1994a). The intensity of cerebellar stimulation should always be adjusted relative to CST activation with foramen magnum level stimulation.

2.3. Triple stimulation technique

2.3.1. TST methodology

The triple stimulation technique (TST) is a collision method, first designed to measure conduction blocks in peripheral nerves and was subsequently adapted to study the corticospinal conduction (Magistris et al., 1999). The TST circumvents problems encountered with TMS. Namely, MEP response are variable in size and smaller than CMAP responses, a phenomenon related to central desynchronization, and thereby precluding a reliable quantitative evaluation of central motor conduction based on MEP amplitude. The desynchronization of descending volleys leads to phase cancellation of motor unit potentials, accounting for the MEP variability and smaller amplitude, even when facilitated with background muscle contractions, when compared to CMAP amplitudes (Magistris et al., 1999, Magistris et al., 1998, Rosler et al., 2002).

The triple stimulation technique (TST) corrects the desynchronization of descending corticospinal volleys and quantify central motor conduction (Magistris et al., 1999, Magistris et al., 1998, Z'Graggen et al., 2005). The proof of concept comes from the resultant MEP amplitude, which corresponds more closely to CMAP amplitudes, with the excitation of entire motor neuron pool innervating the target muscle in healthy subjects (Buhler et al., 2001, Magistris et al., 1998). Triple stimulation technique has become an established tool in clinical practice and research, contributing to a better understanding of motor cortex physiology. When combined with paired pulse stimulation protocols, TST may exclude a role for desynchronization in mediating intracortical inhibition and facilitation (Caranzano et al., 2017).

The principle of TST is explained in Fig. 2. TST consists of three successive stimuli with pre-defined delays. The TMS pulse (1st stimulus) is delivered over the motor cortex, followed by two supra-maximal electrical stimuli delivered to the nerve innervating a target muscle. The first electrical stimulus is delivered distally (2nd stimulus) while the second electrical stimulus is applied proximally (3rd stimulus) with at Erb's point or sciatic nerve at the gluteal fold. In healthy subjects, the descending discharges from TMS collides with antidromic discharges elicited by the 2nd stimulus leading to cancellation. The 3rd stimulus elicits synchronous discharges resulting in a supramaximal CMAP. In central motor dysfunction, the TMS induced descending discharges fail to reach the peripheral axon, either totally or partly, resulting in a paucity of collision with the 2nd stimulus. Consequently, descending discharges from the 3rd stimulus collide with antidromic discharges from the 2nd stimulus resulting in smaller CMAP responses. Commercially available software is available which sets the interstimulus intervals between the three stimuli, ensuring optimal collision, and thereby facilitation the translation of TST into clinical practice.

The TST response is compared to that of a control curve obtained by triple stimulation performed on the peripheral nerve [Erb's point (1st stimulus)-to-wrist (2nd stimulus)-to Erb's point (3rd stimulus)] paradigm. The proportion of spinal motor neuron pool of the target muscle discharged by TMS is quantified by the amplitude ratio of the TST test to the TST control curves. A TST amplitude ratio > 93% can always be obtained in healthy subjects and TST exhibits good test-to-test reliability (Buhler et al., 2001, Humm et al., 2004b, Magistris and Rösler, 2003, Magistris et al., 1999, Magistris et al., 1998). Modified TST protocols correcting for volume conduction of adjacent hand muscles (Ziemann et al., 2004) and an extended TST protocol including a fourth (quadruple) and a fifth (quintuple) stimulus have also been described, enabling a more precise estimate of the number of repetitive spinal motor neuron discharges (Z'Graggen et al., 2005), although these techniques are yet to be applied in clinical practice.

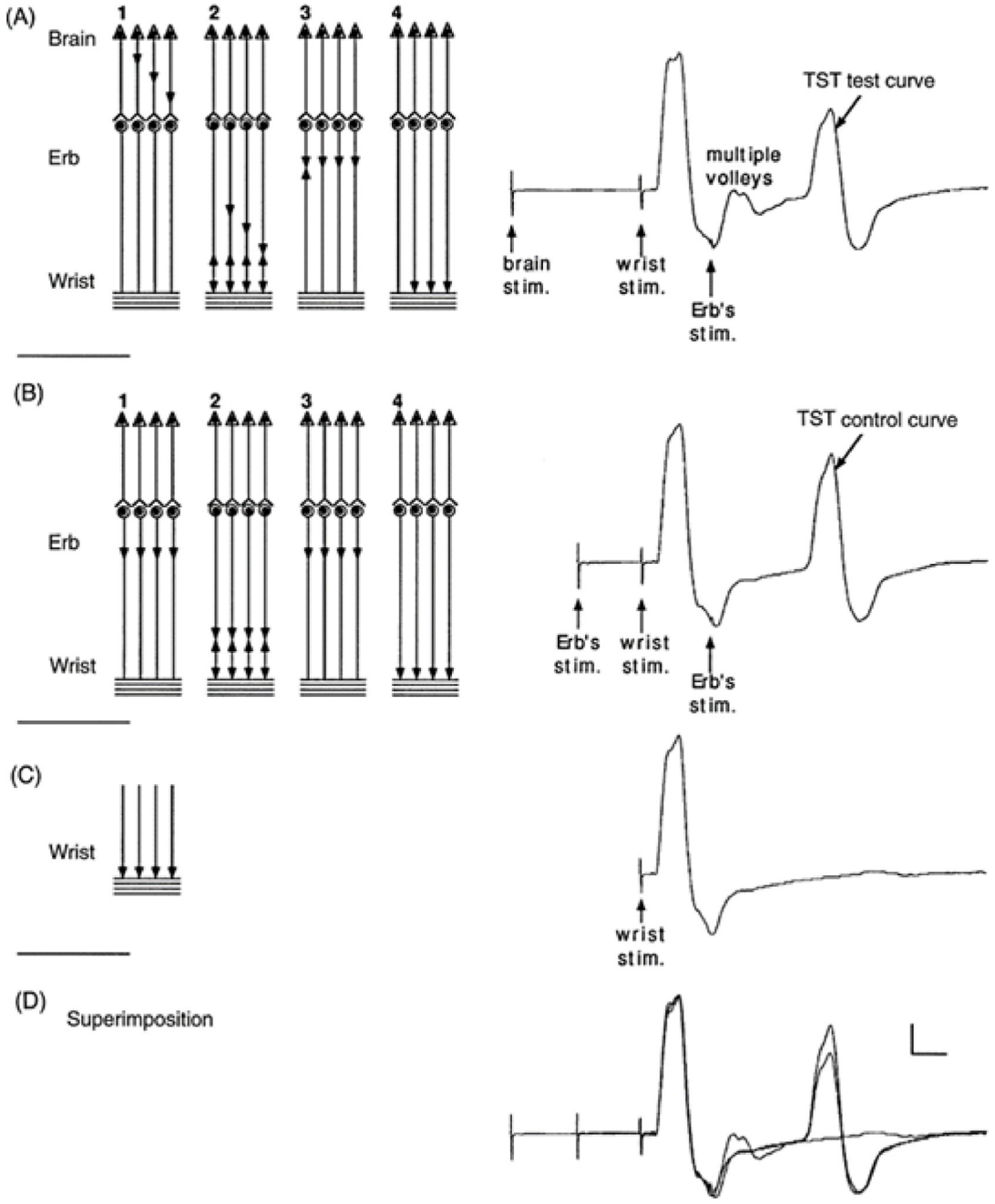

Fig. 2. The triple stimulation test (TST) principle. On the left, a schematic diagram of the motor tract is simplified to four corticospinal axons with monosynaptic connections to four peripheral axons (a simplification which does not account for the complexity of corticospinal connections); horizontal lines represent the muscle fibres of the four motor units. Recordings are shown on the right: **(A)** TST test, **(B)** TST control, **(C)** response to a single stimulus at wrist and **(D)** superimposition of recordings A, B and C. In this example a submaximal transcranial stimulus excites 75% of the axons (three axons out of four). Desynchronization of the three action potentials is assumed to occur within the corticospinal tract (or possibly at the spinal cell level). (**A, 1**) Transcranial stimulation excites three out of four axons. (**A, 2**) After a delay, a maximal stimulus applied to the wrist evokes the first negative (upward) deflection in the TST test trace; this response is followed by that of the multiple-discharge volleys (not figured on the left scheme). (**A, 3**) After a delay, a maximal stimulus is applied to Erb's point; (**A, 4**) a synchronized response from the three axons excited initially by the transcranial stimulus is recorded as the second large deflection of TST test trace. (**B, 1**) A maximal stimulus is applied to Erb's point; (**B, 2**) after a delay, a maximal stimulus applied to the wrist evokes the first deflection of TST control trace; (**B, 3**) after a delay, a maximal stimulus is applied to Erb's point; (**B, 4**) a synchronized response from the four axons is recorded as the second deflection of TST control trace. **(C)** The response evoked by stimulating the wrist serves as a baseline for measurement of the amplitude and area of the second deflection of the TST curves. **(D)** On the superimposed traces, the smaller size of the second deflection of the TST test trace, compared with that of the TST control trace, demonstrates that not all spinal axons of the target muscle were excited by transcranial stimulation (in this example both amplitude and area ratios should be 75% if the four individual MUPs have identical sizes). Calibrations: 2 mV and 5 ms. (*Figure from Magistris, M. R., K. M. Rosler, A. Truffert and J. P. Myers (1998). "Transcranial stimulation excites virtually all motor neurons supplying the target muscle. A demonstration and a method improving the study of motor evoked potentials." Brain 121: 437–450 (with kind permission of the authors and Oxford University Press (*Magistris et al., 1998a*).*).

2.3.2. Clinical utility of TST

TST enables precise quantification of central and peripheral conduction deficits that result from reduced excitability, loss of cortical motor neurons, conduction block in the corticospinal tracts or proximal peripheral motor nerve segments. TST is two to three times more sensitive than standard TMS and may detect even minor deficits (Buhler et al., 2001, Magistris et al., 1999, Magistris et al., 1998). In central demyelinating diseases, TST may quantify temperature-dependent conduction blocks underlying the Uhthoff phenomenon (Humm et al., 2004b). Additionally, TST appears to be reliable in monitoring disease course and effects of therapeutic interventions in multiple sclerosis (Hofstadt-van Oy et al., 2015). Compared to conventional MEP, the TST correlates better with the clinical performance and global disability in patients with multiple sclerosis (Giffroy et al., 2019).

Separately, TST has been proven sensitive in detecting loss of corticomotor neurons in amyotrophic lateral sclerosis, even at a subclinical stage, and in distinguishing central from lower motor neuron degeneration. TST complements the standard neurophysiological evaluation and improves diagnostic accuracy in ALS (Grapperon et al., 2021, Kleine et al., 2010, Komissarow et al., 2004, Rösler et al., 2000, Wang et al., 2019).

In disorders of the peripheral nervous system, particularly multifocal motor neuropathy with proximal conduction block (MMN), TST may differentiate conduction block from temporal dispersion in proximal nerve segments and increases the sensitivity for detecting proximal conduction block from 60% to 90% compared to standard neurophysiological studies (Attarian et al., 2005, Deroide et al., 2007). When combined with neuroimaging (MRI), TST increases the sensitivity for detecting brachial plexus pathology, thereby providing further support for diagnosis of MMN (Corazza et al., 2020). Of relevance, TST may also detect proximal conduction blocks in other peripheral nerve pathologies such as Guillain–Barre syndrome (Taieb et al., 2015) and chronic inflammatory demyelinating polyradiculoneuropathy (Attarian et al., 2015).

TST has also been applied in a number of central nervous system disorders such as Parkinson's disease (Xu et al., 2020), multiple system atrophy (Eusebio et al., 2007) and spinocerebellar ataxia type 6 (Sakuma et al., 2005), although the clinical relevance remains to be determined.

At a clinical level, the use of TST has some caveats. Notably, TST is limited to the study of central conduction to distal hand and foot muscles (Buhler et al., 2001, Magistris et al., 1999, Magistris et al., 1998, Rosler et al., 2002). Absence or marked reduction of CMAP responses preclude TST studies. Additionally, TST cannot differentiate central conduction deficit from proximal peripheral conduction block, and clinical correlation is required. Confounding effects of sub-maximal peripheral stimulation also need consideration (Caranzano et al., 2021). Potential risk of injury with needle stimulation, when used for proximal sciatic nerve stimulation also needs consideration, although this is a rare adverse event. Another major limitation of TST is the fact that the technique is rather painful, limiting its use for monitoring patients' follow-up.

2.4. Other TMS techniques

2.4.1. Foramen magnum stimulation

Activation of the corticospinal tracts (CST) at the foramen magnum was first described with a high voltage electrical stimulation (Ugawa et al., 1991b), and later with TMS using a double-cone coil (Ugawa et al., 1994c). The site of foramen magnum stimulation (FMS) seems to be at either the foramen magnum or CST decussation [cervicomedullary junction] (Ugawa et al., 1992, Ugawa et al., 1991b, Ugawa et al., 1994c), preferentially activated by TMS currents induced in a parallel direction to the decussation (Taylor, 2006). Upward induced currents at foramen magnum are more effective than downward currents (Ugawa et al., 1989), with optimal TMS coil position being mid-way between the inion and mastoid process ipsilateral to the target muscle (Shirota et al., 2011). The MEP latency with FMS is 2–3 ms shorter than D-wave latency and was not impacted by voluntary contraction, contrasting with motor cortical stimulation (Ugawa et al., 1991b, Ugawa et al., 1994c). The physiological differences could relate to the fact that FMS evokes a single descending volley (Taylor et al., 2002, Ugawa et al., 1991b, Ugawa et al., 1994c), in contrast to cortical stimulation that elicits multiple descending volleys by a single pulse stimulation (Day et al., 1987).

The clinical utility of FMS is in localizing the site of CST lesions rostral or caudal to the pyramidal decussation (Ugawa et al., 1996), and the clinical utility was demonstrated in the following settings; (i) detecting subclinical lesions, (ii) identifying multiple CST lesions, (iii) unmasking CST dysfunction that could be clinically masked by presence of peripheral neuropathy, and (iv) establishing the presence of distinct disease-conduction delay rostral to foramen magnum was shown to distinguish cervical myeloradiculopathy from amyotrophic lateral sclerosis (ALS) (Ugawa et al., 1996). Separately, prolonged cortical to brainstem (CTX-BST) conduction times were reported in ALS, although is less sensitive at detecting CST dysfunction than prolonged CMCT (Tokimura et al., 2020). Despite potential clinical utility, FMS has not been used widely due to pain associated with stimulation. Foramen magnum stimulation may fail to elicit an MEP response which could be overcome by a paired-pulse FMS paradigm (Matsumoto et al., 2008), although there is limited clinical experience in using this technique. Separately, FMS may be used to assess the excitability of spinal motor neurons (Taylor, 2006) and spinal cord synaptic efficacy (Cortes et al., 2011, Fitzpatrick et al., 2016, Yamashita et al., 2021), which may be of clinical utility in spinal cord injuries (Vastano and Perez, 2020), although further research is required.

2.4.2. Conus stimulation

Stimulation of the conus enables assessment of the corticoconus motor conduction time (CCCT) and cauda equina conduction time (CECT), which reflect conduction in proximal peripheral nerve segments innervating the lower limbs (Fig. 3). Conus stimulation is achieved by using a large 20-cm-diameter Magnetic Augmented Translumbosacral Stimulation (MATS) coil (Matsumoto et al., 2009b). The MATS coil is positioned lateral to midline and contralateral to recording muscle site. The edge of the MATS coil is placed over the L1, L3 or L5/S1 spinous processes with stimulus intensity set to maximal stimulator output (Matsumoto et al., 2009b). The magnetic stimulation induced currents flowing in either upward or downward direction in the body, and three MEP responses are evoked at different directions of the induced currents. The optimal induced current direction is defined as the direction in which the largest response was elicited with a stable latency (Matsumoto et al., 2010a, Matsumoto et al., 2013a). When recording from the tibialis anterior (TA) muscle (Fig. 3C and D), proximal segments of the cauda equina are activated by positioning the magnetic augmented translumbosacral stimulation (MATS) coil over the L1 spinous process and inducing current flow upward, while neuro-foraminal stimulation is achieved by placing the coil over the L5 spinous process for inducing current flow 45° downward from the horizontal direction (Matsumoto et al., 2009a, Matsumoto et al., 2009b). A similar stimulation set-up was used when recording from the abductor hallucis (AH) muscle (L1 or L3 spinous process and upward induced current, Fig. 3A and B), with the MATS coil placed over the S1 spinous process and induced current flowing 60° downward from the horizontal direction for optimal neuroforaminal activation (Matsumoto et al., 2009a).

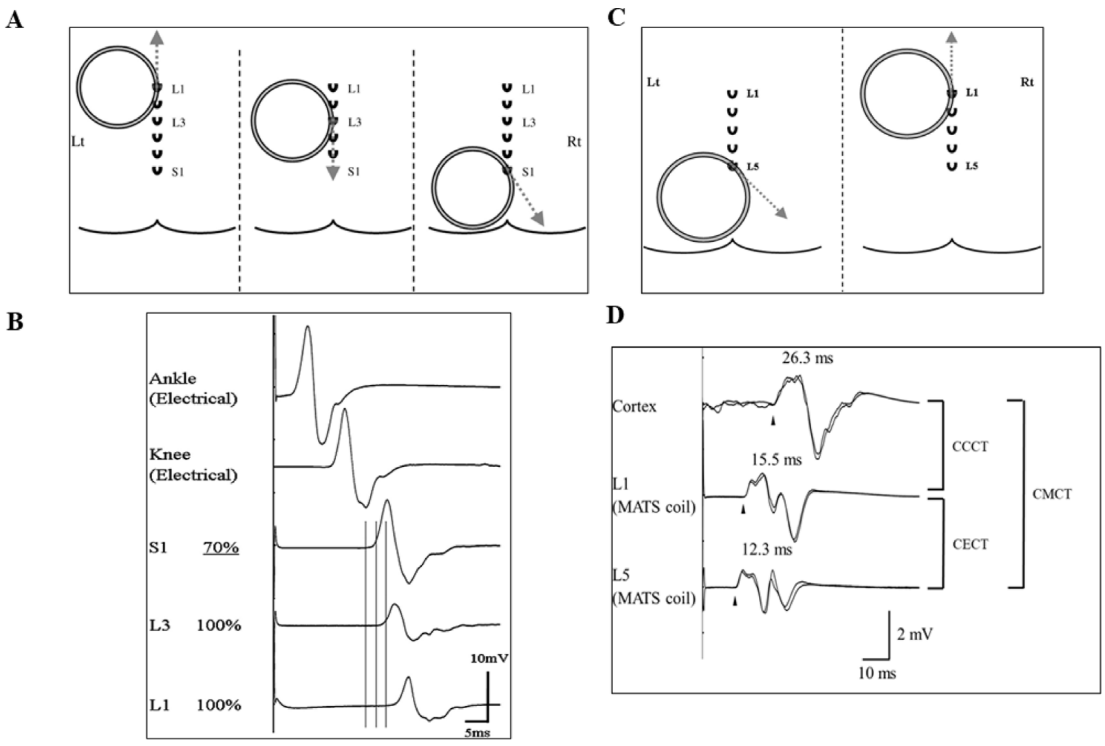

Fig. 3. Stimulation of the lumbosacral region. **(A)** Position of the magnetic augmented translumbosacral stimulation (MATS) coil in magnetic stimulation of cauda equina with motor evoked potentials (MEP) recorded over the adductor hallucis (AH). The coil edge was positioned over the L1, L3, and S1 spinous processes. The induced current directions are illustrated by grey dashed lines and are tangential to the direction of coil winding over the activation sites. **(B)** At L1 and L3 levels, MATS coil stimulations failed to elicit a supramaximal MEP response. At the S1 level, stimulating nerves within the neuro-foramina, the MEP responses are supramaximal elicited at a TMS intensity of 70% maximal stimulator output. The MEP onset latency differences between the L1 and L3 stimulation levels suggest that cauda equina in the spinal canal at L1 and L3 levels were activated separately. Cauda equina conduction time (CECT) is calculated by subtracting the S1 from L1 elicited MEP onset latencies when recoding from AH. Tibial nerve compound muscle action potential (CMAP) responses were illustrated with ankle and knee stimulation. **(C)** Conus stimulation method when recoding over the right tibialis anterior muscle. For proximal cauda equina stimulation, the edge of MATS coil is positioned over the L1 spinous process for inducing currents in an upward direction (dashed grey arrow), while for neuroforaminal activation the edge of the MATS coil is positioned over L5 with induced current direction being 45° downward from a horizontal direction. **(D)** The MEP responses elicited with cortical, L1 and L5 stimulation are illustrated. The cortico-conus motor conduction time (CCCT) is calculated by subtracting the MEP onset latency elicited by L1 from cortical stimulation. Additionally, CECT is measured by subtracting MEP onset latency elicited by L1 form L5 stimulation. Central motor conduction time (CMCT) is represented by addition of CCCT and CECT.

The CECT is calculated by subtracting the L5/S1 evoked MEP latency from that evoked at the L1 level. The CCCT is calculated by subtracting the MEP latency evoked with L1 from motor cortical stimulation, while central motor conduction time can be calculated by subtracting MEP latency at L5/S1 stimulation from cortical MEP latencies (Matsumoto et al., 2010a, Matsumoto et al., 2013a). A limitation of conus stimulation relates to submaximal activation of neural elements, thereby limiting the possibility of establishing conduction block at the cauda equina.

At a clinical level, assessment of CCCT may identify CST dysfunction in the setting of peripheral nerve disease or when upper motor neuron signs are absent (Murakami et al., 2019, Tokimura et al., 2020, Tokushige et al., 2013). Separately, CECT may be prolonged in demyelinating neuropathies, such as chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating Guillain-Barré Syndrome phenotypes, anti-myelin-associated glycoprotein (MAG) polyneuropathy, POEMS syndrome and Charcot-Marie-Tooth disease type 1 (Maccabee et al., 2011, Matsumoto et al., 2015, Matsumoto et al., 2010b), where it may be of diagnostic utility. Additionally, prolonged CECT was also reported in primary malignant lymphoma of the cauda equina (Matsumoto et al., 2009a) and in lumbar spinal canal stenosis (Senocak et al., 2009). Larger studies are required to determine the diagnostic utility of conus stimulation in peripheral nervous system disorders, particularly developing optimal diagnostic cut-off criteria.

2.4.3. Facial nerve stimulation

The facial nerve can be directly stimulated by TMS with a 90 mm circular coil positioned over the ipsilateral parieto-occipital region, with the base of the coil over the mastoid process (***canalicular stimulation***) (Chen et al., 2008, Rimpiläinen et al., 1993, Rösler et al., 1989, Schmid et al., 1992, Schriefer et al., 1988, Wolf et al., 1995). The site of facial nerve stimulation remains controversial, although appears to be within the internal acoustic meatus where the nerve transitions from low-resistance cerebrospinal fluid to high-resistance petrous bone (Schmid et al., 1992). Cortical MEPs are elicited by stimulation of the facial area in the contralateral motor cortex, with the optimal position being ~ 2 cm lateral and ~ 1 cm anterior to the position that evokes the strongest contraction in hand muscles (Paradiso et al., 2005). Facilitation of the target muscle is often required to record an MEP response (Rösler et al., 1989). The TMS elicited responses are compared to facial nerve CMAP responses evoked by electrical stimulation at the stylomastoid fossa or further along the facial nerve. The three stimulation sites allow assessment of three segments (cortico-proximal, transosseal, and distal) of the cortico-facial projection.

The MEP and CMAP responses may be recorded from any facial muscle, including orbicularis oculi, oris, nasalis, mentalis, and buccinator, and should be recorded bilaterally to enable a side-to-side comparison. The facial MEP responses are smaller than CMAP

responses, and may be contaminated by a number of artefacts, including volume conduction from uncrossed ipsilateral MEPs, blink and other facial reflexes, peripheral stimulation of the ipsilateral facial nerve, and possibly by activation of muscles innervated by the trigeminal nerve (Paradiso et al., 2005, Türk et al., 1994, Urban et al., 1997). Normative values have been previously reported and should be established with each laboratory prior to undertaking studies in neurological diseases (Rimpiläinen et al., 1992, Rösler et al., 1989, Rösler et al., 1995, Urban et al., 1997). The clinical utility of magnetic stimulation in facial nerve disorders is discussed below.

2.4.4. Spinal nerve stimulation in peripheral neuropathy

The spinal nerve stimulation is sometimes used to evaluate the proximal parts of peripheral nerves. Focal lesions between Erb's point and neuroforamina, i.e., brachial plexus or spinal nerves just distal to neuroforamina, can be detected in demyelinating neuropathies (Matsumoto et al., 2013a, Matsumoto L. et al., 2010), and focal lesions between knee and neuroforamina, i.e., the sacral nerves, sacral plexus, or spinal nerves just distal to neuroforamina, can also be detected (Matsumoto et al., 2013b).

2.5. TMS-EEG

TMS in combination with EEG (TMS-EEG) enables direct assessment of cortical circuits, by-passing sensory and motor pathways, as TMS-EEG is not reliant on the integrity of these systems. Moreover, TMS-EEG can activate cortical neurons with a wide range of stimulation intensities, thereby providing full excitability profiles, from threshold to saturation (Casali et al., 2013, Kähkönen et al., 2005, Komssi et al., 2004, Rosanova et al., 2009). Consequently, input–output properties of cortical neurons and circuits can be better assessed, which has pathological implications. Additionally, TMS-EEG offers an unambiguous measure of connectivity, namely causal interactions within the thalamocortical system (Massimini et al., 2005, Morishima et al., 2009, Paus, 2005).

The flexibility of TMS-EEG affords unprecedented opportunities for exploring and modulating cortical excitability but also represents a challenge, especially when probing cortical areas outside M1. Indeed, in the absence of a motor read-out, when a TMS coil is positioned over the region of interest, the actual impact of the induced electric field on cortical neurons is difficult to predict, even when utilizing individual head models and TMS navigation systems (Lioumis and Rosanova, 2022). Key factors such as microscale axon orientation, cytoarchitectonics and local neuronal excitability remain unaccounted for and may dramatically affect the interaction between the induced electric field and brain activity. Differences in the strength of direct cortical activation have been highlighted as a major problem affecting the reproducibility of TMS-EEG studies in assessing cortical excitability and connectivity (Belardinelli et al., 2019). Maximizing the direct impact of stimulation on cortical neurons, while minimizing collateral effects such as cranio-facial muscle, auditory or somatosensory activation, is a key prerequisite for improving the reproducibility, signal-to-noise ratio (SNR), as well as clinical utility of TMS-EEG.

Although off-line software tools are available for reducing artifacts (Mutanen et al., 2022), controlling for quality of EEG signals in real-time is the most effective strategy for recording reliable TMS evoked potentials (TEP). Utilizing a software that enables setting of stimulation parameters based on real time visualization EEG signals, may be critical for recording good quality TEPs, and has been successfully implemented in the study of brain-injury patients (Casali et al., 2013, Casarotto et al., 2016, Rosanova et al., 2018, Sinitsyn et al., 2020). A free-release MATLAB-based tool, called rt-TEPs (real-time TEP), is available to assist in the implementation of this approach (Casarotto et al., 2022).

Together with tools that enable on-line assessment of TEP quality, other tools have been developed to control for confounding factors such as the auditory evoked potentials (AEP) produced by TMS "clicks". The AEPs can be abolished by continuously playing a white noise through inserted earplugs during acquisition of TEPs (Paus et al., 2001), administering continuous masking noise that reproduces the time-varying spectral content of the coil "click" (Massimini et al., 2005), or by interposing a foam layer between the TMS coil and scalp (ter Braack et al., 2015). More recently, a highly flexible and freely available tool that can generate effective and safe masking noises, customized for each TMS device and tailored on subject's perception, has been released (Russo et al., 2022).

Developing such tools is critical as researchers and clinicians would like to avoid situations such as that illustrated in Fig. 4. Here, it is shown how despite reasonable a priori assumptions based on anatomical and biophysical data, TMS can have little impact on the underlying cortex. Under these circumstances, lack of real-time control on cortical impact, artifacts and confounding factors may result in a 'false TEP' with little initial activation and late symmetrical, central topography typical of an AEP. The figure also shows how this fundamental drawback can be readily controlled for and prevented during the experiment if the operator's actions during the measurement are informed by tools such as rt-TEP. In this case, responses consistent with the effect of direct cortical stimulation can be easily obtained, and are characterized by a strong initial activation under the TMS coil followed by asymmetric topography, which is specific to the stimulated site, and high SNR.

To obtain high-quality TEPs, the adjustment of TMS parameters may involve noise masking optimization, intensity changes and small coil rotations (as illustrated in Fig. 4). Although a few manual rotations of the TMS coil are generally effective in increasing the SNR, a systematic search of the optimal electric field orientation is practically unfeasible. Such fine tuning requires more sophisticated strategies and hardware, such as an EEG-based adaptive search algorithms coupled with electronically controlled two-coil transducers (Souza et al., 2022, Tervo et al., 2020, Tervo et al., 2022). Combining rt-TEP with advanced closed-loop systems represents a promising strategy whereby fundamental stimulation parameters are first set by the operator, based on visual feedback, and then automatically optimized in a closed-loop fashion.

Beside the appropriate experimental procedures, the reliability of TMS-EEG measurements critically depends on the hardware. Active amplifiers tend to induce long-lasting decay artifacts that are more prominent and difficult to eliminate, often masking early TEPs components. The accuracy of the TMS-navigation unit is also a key factor. Specifically, the settings (coil position coordinates and rotation) identified during the initial parameter search must be precisely retrieved and held steady throughout the experiment and across repeated measurements (Lioumis and Rosanova, 2022). TMS hardware, TMS coils and pulse waveshapes can differ in their focality, efficacy on stimulating cortical circuits and collateral effects (*magnetic artifacts, sensory and auditory stimulation*) (Koponen et al., 2020). With theoretical and technical improvements, the quality and informativeness of TEPs is likely to improve.

2.5.1. Clinical measurements: Principles and examples

Experimental procedures and tools to record reproducible TEPs are being improved, standardized and shared within the TMS-EEG community (Belardinelli et al., 2019, Siebner et al., 2019) with the aim of establishing TMS-EEG as a reliable clinical tool (Julkunen et al., 2022). Recent preclinical studies have suggested that several biomarkers can be already extracted from TEPs that may serve as potential pathophysiological, diagnostic, and prognostic biomarkers in neurological patients (Tremblay et al., 2019).

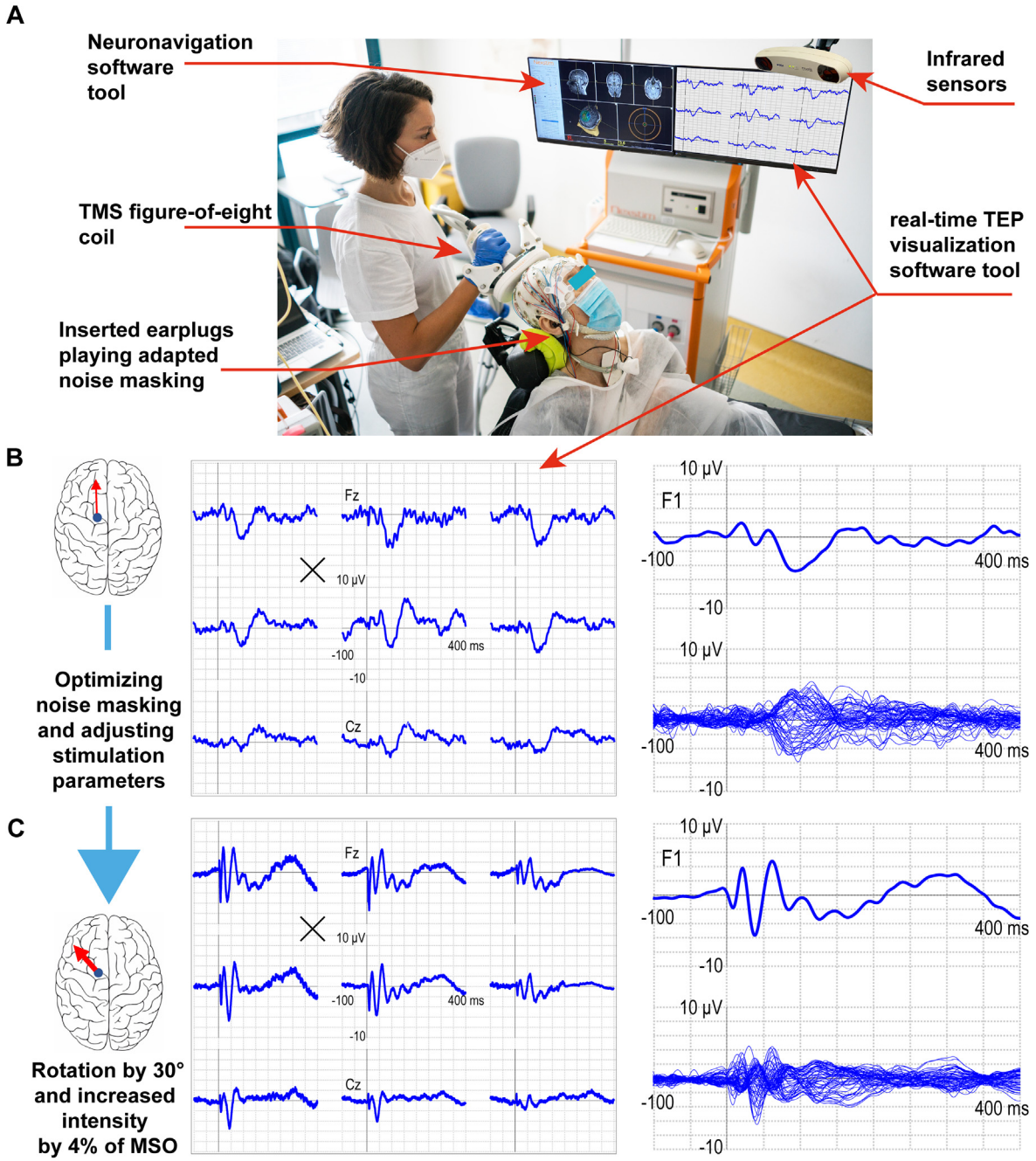

Fig. 4. TMS-EEG principles. (A) Key elements (pointed by red arrows) of a TMS-EEG set-up employed in a clinical setting. (B and C) These panels directly compare the final average TMS evoked potentials [(TEP] (150 trials) collected during two sessions. Although both responses have been obtained by setting stimulation parameters based on reasonable a priori anatomical (position and orientation with respect to the cortical gyrus) and physiological (maximum stimulator output [MSO, %] at or above resting motor threshold [RMT]) information, they differ in fundamental ways. The responses in B show small early activations and are characterized by larger, late symmetric components which are maximal over midline channels, like those reported previously (Conde et al., 2019; Chung et al., 2018). These waveforms are hardly consistent with the effects of direct cortical stimulation, which is expected to trigger responses that are large immediately after the pulse and specific for the stimulation site (Keller et al., 2014; Kundu et al., 2020). Conversely, the TEP reported in C fulfills these basic criteria and is similar to those described in previous studies (Rosanova et al., 2009; Casarotto et al., 2016; Sinitsyn et al., 2020). In this case, a strong initial activation is followed by an overall asymmetric wave shape with high signal-to-noise ratio (SNR). Obtaining this kind of responses only required maximizing the immediate impact of TMS on early (8–50 ms) components through slight adjustments of the intensity (by 4% MSO) and orientation of stimulation (30○ counterclockwise), while at the same time optimizing noise masking. Making such adjustments is relatively straightforward but would be impossible based on a priori information alone and can only be done if the operator is guided in real-time by informative visual feedback (rt-TEP) about the immediate effects of TMS.

2.5.1.1. Time-domain, early and late components. Early TEP components (0–50 ms) have been considered as markers of cortical excitability, possibly reflecting the immediate reactivity of local cortical neuronal populations (Moliadze et al., 2003, Mueller et al., 2014, Romero et al., 2019). Among different time-domain measurements, the peak-to-peak amplitude and slope of early TEPs at the individual channel level, as well as multi-channel measurements such as local and global mean field power in early time windows, have been used to detect changes in cortical excitability over time or after neuromodulatory interventions (Esser et al., 2006, Huber et al., 2013, Ly et al., 2016, Romero Lauro et al., 2014). Amplitude changes of early TEPs and regional cortical hyperex-

citability have been demonstrated in Alzheimer's disease at specific cortical locations, suggesting potential clinical utility (Casarotto et al., 2011, Casula et al., 2022, Julkunen et al., 2011, Julkunen et al., 2008), although the variation in cortical atrophy across studies may limit interpretability given the inherent variability of stimulation parameters. Early TEPs have a high individual test–retest reproducibility (Casarotto et al., 2010), and may be of utility in assessing disease progression or treatment effects in neurological diseases. Of relevance, early TEPs have been effectively used to measure the increase in frontal cortex excitability induced by electroconvulsive treatment (Casarotto et al., 2013) and local modulations of cortical excitability by dopaminergic agents in Parkinson's disease (Casarotto et al., 2019, Leodori et al., 2022, Turco et al., 2018c).

Selective alterations of late TEPs components (>50 ms) have been linked to pharmacological modulation of cortical inhibition (Premoli et al., 2014), or pathological cortical adaptation dynamics in severe brain injury (Rosanova et al., 2018) and stroke (Sarasso et al., 2020, Tscherpel et al., 2020). Abnormalities of later TEP components have been observed in Parkinson's disease (Maidan et al., 2021), whereas deep brain stimulation of the subthalamic nucleus and L-Dopa intake increases late TEPs (Casula et al., 2017). Finally, alterations of late TEP components may be of utility as a biomarker of epileptogenic cortical foci and a measure of anti-epileptic drug effects (Kimiskidis et al., 2017, Valentin et al., 2008).

2.5.1.2. Spectral features. Alterations in membrane properties of cortical and thalamic neurons, as well as alterations in their patterns of connectivity, underlie most neurological conditions, leading to distinctive changes in oscillatory dynamics (Hughes and Crunelli, 2005, Jeong, 2004, Llinás et al., 1999, Soininen et al., 1992). Such alterations can be studied with EEG recordings, although spontaneous rhythms are variable and their topography can change radically in response to eye opening, planning of simple movements or cognitive activity. A complementary way of probing frequency tuning of brain circuits is to apply direct perturbations to detect the main rate of ensuing oscillations, the so-called natural frequency. Following an early (0–20 ms) stereotypical sharp component, TMS consistently evokes (i) alpha-band oscillations after stimulation of the occipital cortex, (ii) beta-band oscillations after stimulation of the parietal cortex, and (iii) fast beta/gamma- band oscillations after stimulation of the frontal cortex (Rosanova et al., 2009). Dampening of beta-band responses have been reported in Parkinson's disease after unilateral surgical lesioning of the ventrolateral thalamic nucleus (Van Der Werf et al., 2006). A marked reduction of gamma-band TMS-evoked oscillation was reported in the frontal cortex of schizophrenia patients, possibly related to thalamic dysfunction (Ferrarelli et al., 2012, Guller et al., 2012). Slowing of the natural frequency was reported in cortical areas overlying subcortical strokes (Pellicciari et al., 2018, Sarasso et al., 2020, Tscherpel et al., 2020). As such, TMS-evoked EEG oscillations may provide valuable clinical information about the state of cortico-subcortical (especially thalamic) loops.

2.5.1.3. Connectivity. Long-range interactions of neuronal populations represent a key aspect of brain function. Such interactions are typically inferred based on measures of functional connectivity that rely on correlation-based analyses of spontaneous activity. A limitation of these measures of temporal correlation among time series, such as cross-correlation, coherence, phase-locking value, is the possible biasing by common drivers, correlated inputs, and noise. A more informative and clinically relevant measure is ***effective connectivity***, which refers to the ability of a specific neuronal population causally influencing the activity of connected neuronal groups within a system (Friston, 2011, Lee et al., 2003). TMS-EEG offers a straightforward way to measure effective connectivity in the human brain.

In studies of patients with severe brain injury, resulting in an Unresponsive Wakefulness Syndrome (UWS), a dramatic reduction in spread of TMS-evoked activity has been reported both at the source and sensory level (Casarotto et al., 2016, Ragazzoni et al., 2013, Rosanova et al., 2012). Notably, recovery of effective connectivity paralleled and often heralded recovery of consciousness. Changes in effective connectivity have also been demonstrated in stroke (Borich et al., 2016, Casula et al., 2021) and genetic generalized epilepsy patients (Vlachos et al., 2022), whereas no major variations were found in early-stage patients with multiple-sclerosis (Zipser et al., 2018). Clinical results show that perturbational measures of connectivity with TMS-EEG are sensitive and potentially prognostic, especially after diffuse, multifocal and focal brain injury. A potential role for TMS-EEG assessing and prognosticating mild traumatic brain injury has been recently proposed (Coyle et al., 2018).

2.5.1.4. Complexity. The TEPs are characterized by high differentiation (i.e., different areas have different natural frequencies) and high integration (i.e., causal interactions among distant areas). Inspired by theoretical principles, TMS-EEG-based measures of complexity have been developed to simultaneously quantify differentiation and integration in corticothalamic networks. These measures have been clinically utilized by different centers in large patient cohorts, representing a novel approach to stratifying Disorders of Consciousness (DoC) (Casarotto et al., 2016, Sinitsyn et al., 2020, Wang et al., 2022) and will be discussed below in section 3.12.

2.6. Peristimulus time histogram (PSTH)

The PSTH TMS technique assesses corticomotoneuronal system integrity by evaluating a small number of corticomotoneurons that converge onto a specific population of spinal motor neurons (Weber and Eisen, 2000). The primary peak (PP) reflects the firing probability of a single voluntarily recruited motor unit induced by a sub-threshold TMS stimulus. In healthy controls, PP occurs ~ 20–25 ms after the stimulus, is well synchronized and of short duration, in keeping with activation of fast-conducting monosynaptic pathways. The PP reflects the rising edge of the underlying excitatory post-synaptic potential (EPSP) evoked at the anterior horn cell. Additionally, excitatory, and inhibitory effects on motor neurons may be assessed, as can the strength of synaptic inputs. Latency, amplitude, and dispersion (calculated by bins excess, duration, and synchronicity) of the PP is typically evaluated (see Table 1).

3. TMS abnormalities in neurological diseases (Table 1)

3.1. Neurodegenerative disorders

3.1.1. Amyotrophic lateral sclerosis/motor neuron disease

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder of the human motor system characterized by upper [UMN] and lower motor neuron [LMN] dysfunction (Kiernan et al., 2011, Kiernan et al., 2020). Fundamental to understanding of ALS pathogenesis pertains to the relationship between upper and lower motor neuron dysfunction. An UMN origin for ALS has been proposed, whereby corticomotoneuronal hyperexcitability mediated neurodegeneration via an anterograde glutaminergic mechanism, the *dying forward hypothesis* (Eisen et al., 1992). In contrast, LMN dysfunction has been proposed as the primary event in ALS pathogenesis with UMN dysfunction occurring as a secondary phenomenon [*dying-back hypothesis*] (Fischer et al., 2004,

Table 1
Clinical diagnostic utility of TMS in neurological diseases: Consensus opinion.

Disease	Characteristic TMS findings	Potential Clinical Utility	Clinical aspects that may affect interpretation
Amyotrophic lateral sclerosis (ALS)	SICI ↓ SICF ↑ ICF ↑ ←→ RMT←→ ↓ ↑ MEP/CMAP amplitude↑ or ↓* CSP duration ↓ CMCT ↑	-SICI is a potential diagnostic biomarker in differentiating ALS from mimicking disorders -Useful in differentiating ALS from other neuromuscular mimicking disorders -CMCT prolongation detects the CST involovements in patients with muscular atropy due to spinal motor neuron involvements.	-Riluzole therapy may transiently increase SICI -Changes in cortical excitability according to disease progression
Parkinson's disease (PD)	SICI ↓ SICF ↑ ICF ←→ ↓ RMT ←→ ↓ (PD subtype) I/O curve steeper at resting state SAI ↓ (disease progression) CSP duration ←→ ↓ ISP duration ←→ ↓ (PD subtype) Normal SICI on I3 waves	-SICI and SICF might be used as biomarkers of disease progression -SAI might be used to predict PD dementia and falls -Limited diagnostic utility	-ON or OFF-drug condition -Tremor-dominant or akinetic-rigid subtype -Disease duration or severity of symptoms
Parkinsonism (MSA, PSP)	CMCT ↑ (MSA, PSP) SICF←→	-Prolonged CMCT might be used to differentiate MSA/PSP from PD -Limited diagnostic utility	-Parkinsonism or cerebellar ataxia predominant MSA subtypes
Lewy Body Disease	SICI ↓ ICF ↓ SAI ↓	-SAI may help differentiate LBD (SAI ↓) from Parkinsonian syndrome and FTD (SAI←→) -Limited diagnostic utility	
Huntington's disease (HD)	SAI ↓ SICI ←→ ↓ CSP duration ↑ (early stage)	-Limited diagnostic utility	-Different charges according to disease stage -HD patients are not able to be fully relaxed
Dystonia	SICI ↓ LICI ↓ CSP ↓ IHI ↓ (with mirror movements) Surround inhibition ↓	-Limited diagnostic utility	-Test on affected side or unaffected side -Homogeneity of dystonia presentation –No single parameter can be used to prove organic dystonia
Tics and Tourette's syndrome	SICI ↓ CSP duration ↓	-Limited diagnostic utility	-Timing of assessment (before tics occur or when tics are suppressed)
Cervical spondylitic myelopathy	CMCT ↑ MEP amplitude ↓	-Prolonged CMCT is a major and objective criterion for the diagnosis of pyramidal tract lesion in the context of myelopathy	MEP of APB muscle is most sensitive
Spinal cord injury	RMT ↑ CMCT ↑ MEP amplitude ↓	-Prolonged CMCT is a major and objective criterion for the diagnosis of pyramidal tract lesion in the context of myelopathy	-No single measurement can predict gait and balance outcome after SCI
Alzheimer's disease (AD)	RMT ↓ AMT ↓ CSP duration ←→ SICI ←→ ICF ←→ LICI ←→ SAI ↓	-Potential diagnostic utility -SICI-ICF/SAI ratio may help differentiate AD from FTD -SICI-ICF may help differentiate AD from LBD	-SAI may be increased by acetylcholinesterase inhibitors
Mild cognitive impairment due to Alzheimer's disease	RMT ↓ SICI ←→ ICF ←→ LICI ←→ SAI ↓	-Potential diagnostic utility -SICI-ICF/SAI ratio may help differentiate MCI-AD from MCI-FTD -SICI-ICF may help differentiate MCI-AD from MCI-LBD	-Interpretation may be hampered by the heterogeneity of MCI and the paucity of studies performed in patients with a biomarker supported diagnosis of MCI
Frontotemporal dementia (FTD)	RMT ←→ CMCT ↑ SICI ↓ ICF ↓ SAI ←→	-Potential diagnostic utility -SICI-ICF/SAI ratio may help differentiate FTD from AD -SAI may help differentiate FTD from LBD	
Epilepsy	RMT ←→ CSP duration ↑ SICI ↓ ICF ←→	↓ SICI and LICI may be useful in discriminating seizure from syncope Follow up clinical condition	-Antiepileptic medications cause ↑RMT, SICI & LICI

(*continued on next page*)

Table 1 (*continued*)

Disease	Characteristic TMS findings	Potential Clinical Utility	Clinical aspects that may affect interpretation
	LICI ↓		
Myoclonus epilepsy	SICI ↓ SICI ↓ even on I3 waves RMT ↓	-Limited diagnostic utility	Anti-epileptic drugs affect the results
Migraine without aura	SICI ↓ (at ISI 4 ms) SICF ←→SICF ↑ (suprathreshold conditioning stimulus; weak test stimulus) SICF ↓ (preictal phase) RMT←→ ↓ ↑ LICI ←→ (up to 120 ms ISI)LICI ↓ (150% test stimulus)LICI ↓ (250 ms ISI) SAI ←→ SAI ↓ (preictal phase) CSP ←→ (interictal)CSP duration ↓ (interictal, women)	-TMS changes vary according to the phase of migraine cycle -Limited diagnostic utility	-RMT/PT, and SAI change with proximity of migraine attack -ICF changes with conditioning/test stimulus intensity and proximity of migraine attack -CSP duration decreases with focused sustained attention and sleep restriction
Migraine with aura	SICI ↓ SICF ↑ RMT←→ Steeper I/O curve at rest CSP duration ↓ LICI 250 ms ↑ CBI↓ SAI ↓ (when disease progressed)	-PT might be used to discriminate between transient ischemic attacks and aura without headache	-1 Hz rTMS reduces PT - deficits of cortical inhibition are related more to aura rather than headache mechanisms -CSP shortens also in facial muscles -Topiramate modulates occipital cortex excitability
Chronic migraines	RMT↓ SICI absent	-Limited diagnostic utility -Potential biomarker of treatment effects	Botulinum toxin therapy partially normalizes SICI after 12-months treatment
Episodic cluster headaches	SICI ↓ (ictal) SICI ↓ (allodynia) SICF ↑ (preictal and ictal) SICF ↑ (allodynia) RMT ←→ CSP duration ←→	-Limited utility	Changes in paired-pulse TMS variables are ipsilateral to the pain side; inhibitory changes are ictal; facilitatory changes are both interictal and ictal.
Medication-overuse headache	CSP duration ←→ (NSAIDs alone or in combination)CSP duration ↓ (triptans)	-Limited utility	-CSP changes reveal medication-induced neural adaptation in motor cortex
Multiple Sclerosis	CMCT ↑ TST ↓MEP amplitude ↓ (or desynchronized) TST-MEP amplitude ↓	-CMCT increase or MEP amplitude decrease after fatiguing exercise -SICI ↓ -SICF ↓ -SAI ↓ -CSP duration ↑ -ISP ↑ -Limited diagnostic utility -Potential prognostic utility	-TMS measures may be affected by multiple sclerosis type (RRMS vs. SPMS/PPMS), and treatment (corticosteroids and immunomodulatory drugs) and the presence of fatigue
Neuropathic pain	SICI ↓ (contralateral to pain side)	-SICI might be a biomarker to select candidates for analgesic cortical neuromodulation -Limited diagnostic utility	-Defective SICI can be restored by therapeutic intervention producing analgesic effects
Stroke	RMT ↑ MEP latency ↑ MEP amplitude ↓ Shallower I/O curves SICI ↓	-Potential prognostic utility: Absent upper limb MEPs predicts worse motor recovery and outcomes	-Depending on post-stroke phase (acute, sub-acute, or chronic)
Cerebellar disease	CBI ↓	-Differentiate cerebellar ataxia due to cerebellar or cerebellar efferent pathways dysfunction from that due to cerebellar afferent pathways dysfunction, or from non-cerebellar ataxia	-CBI changes may be seen for compensation of basal ganglia dysfunction (movement disorders)

Table 1 (*continued*)

Disease	Characteristic TMS findings	Potential Clinical Utility	Clinical aspects that may affect interpretation
Facial nerve disorders	MEP ↓ or absent Prolonged transosseal conduction time	-May localize facial nerve dysfunction-Prognostication (if MEP present better prognosis) -Limited diagnostic utility	
Brain Tumors	RMT ↑ or ↓ (tumor hemisphere compared to contralateral hemisphere) MEP latency ↑ MEP amplitude ↓	-Preoperative brain mapping -Seed regions for function-based tractography -Preoperative risk stratification -Postoperative transcallosal disinhibition -Limited diagnostic utility	-Edema -Patient cooperation
Functional neurological disorders (paretic disorders)	RMT, SICI, ICF ⟷ RMT, SICI ↑ MEP duration with voluntary contraction ⟷ MEP amplitude with movement imagination ↓	-Change in MEP amplitude with movement imagination -Elemental measures in functional dystonia are similar to other types of dystonia -Limited clinical utility	
Dystonic functional neurological disorders	SICI ↓ LICI ↓ CSP duration ↓ Forearm reciprocal inhibition ↓ Cutaneous silent period ↑	-Limited clinical utility in differentiating functional from organic dystonia	Neurophysiological measures in functional dystonia are similar to other types of dystonia.

APB: Abductor pollicis brevis, CBI: Cerebellar inhibition of the motor cortex, CMCT: Central motor conduction time, CSP: Cortical silent period, GABA: Gamma-aminobutyric acid, LBD: Lewy body disease, IHI: Interhemispheric inhibition, I/O curve: Input-output curve, ISP: Ipsilateral silent period, LICI: Long-interval intracortical inhibition, MEP: Motor evoked potential, MSA: Multiple system atrophy, PPMS: Primary progressive multiple sclerosis, PSP: Progressive supranuclear palsy, RMT: Resting motor threshold, PT phosphene threshold; NSAID (nonsteroidal anti-inflammatory drugs): RRMS: Relapsing-remitting multiple sclerosis, SAI: Short latency afferent inhibition, SCI: Spinal cord injury, SICF: Short-interval intracortical facilitation, SICI: Short-interval intracortical inhibition, SPMS: Secondary progressive multiple sclerosis, TST: Triple-stimulation technique. ⟷, no change or normal; ↓, reduced; ↑, increased. *, The MEP amplitude, expressed as a percentage of the compound muscle action potential response (MEP/CMAP), is increased in strong limbs without marked UMN signs, and also in the early stages of ALS. In most ALS patients, the MEP amplitude patients is decreased. ***It should be stressed that a Delphi consensus process was not possible***.

Williamson and Cleveland, 1999), while others have suggested that upper and lower motor neuron degeneration occur independently and in a stochastic manner [*independent degeneration hypothesis*] (Ravits et al., 2007). Additionally, identification of upper and lower motor neuron dysfunction is critical for ALS diagnosis (Shefner et al., 2020). Transcranial magnetic stimulation has provided vital insights in the understanding of ALS pathogenesis and has emerged as an important diagnostic technique. Early reports described hyperexcitability of motor cortex with lower-than-normal motor threshold, in particular recruiting the same motor units contributing to spontaneous fasciculations (Caramia et al., 1991).

Paired-pulse TMS studies have consistently identified cortical hyperexcitability as a pathogenic mechanism in ALS (Fig. 1), mediated by a combination of reduced cortical inhibition and increased cortical facilitation (Vucic et al., 2018). Reduction or absence of SICI has been identified as an early and intrinsic feature in ALS (Blair et al., 2010, Hanajima et al., 1996, Sommer et al., 1999, Stefan et al., 2001, Tankisi et al., 2022, Vucic and Kiernan, 2006, Vucic and Kiernan, 2008, Yokota et al., 1996, Zanette et al., 2002b, Ziemann et al., 1997b), correlating with peripheral neurodegeneration (Vucic and Kiernan, 2006) and preceding the development of LMN dysfunction (Menon et al., 2015). Reduction of SICI is an adverse prognostic biomarker in ALS (Shibuya et al., 2016b), is associated with disease evolution (Dharmadasa et al., 2020, Menon et al., 2017, Shibuya et al., 2017) and development of clinical features such as the split hand-phenomenon (Bae et al., 2014, Menon et al., 2014). Additionally, SICI reduction is evident in clinically pure lower motor neuron ALS phenotypes, including flail arm and leg variants of ALS (Menon et al., 2016, Vucic and Kiernan, 2007), where it is an adverse prognostic biomarker. It has been argued that the reduction in SICI may represent a compensatory mechanisms in response to peripheral neurodegeneration (Zanette et al., 2002b), although the findings of normal cortical excitability in ALS mimicking disorders (Menon et al., 2015, Vucic et al., 2011b, Vucic and Kiernan, 2008, Vucic et al., 2010), along with partial and transient normalization of SICI with the anti-glutaminergic agent riluzole (Geevasinga N. et al., 2016a, Vucic et al., 2013a), argues against a compensatory mechanism in ALS. Dysfunction or degeneration of GABAergic interneuronal circuits, acting via $GABA_A$, was postulated to mediate the reduction of SICI in ALS (Clark et al., 2021, Nihei et al., 1993, Zhang et al., 2016).

Increased activity of cortical facilitatory circuits also contribute to development of cortical hyperexcitability and ALS pathogenesis. Short interval intracortical facilitation, a biomarker of cortical excitatory circuit function (Di Lazzaro et al., 1999c, Rusu et al., 2014, Van den Bos et al., 2018), is increased in ALS and accompanied by reduction in SICI (van den Bos et al., 2018). Overactivity of facilitatory circuits correlated with a greater degree of functional disability and development of UMN signs.

A comparable increase in cortical hyperexcitability has also been reported in familial ALS cohorts, including phenotypes linked to mutations in superoxide dismutase-1 (Vucic et al., 2008), fused in sarcoma (Williams et al., 2013) and c9orf72 genes (Geevasinga Nimeshan et al., 2015). Significant correlations between cortical hyperexcitability and LMN dysfunction has been established (Geevasinga Nimeshan et al., 2015, Vucic and Kiernan, 2010), with asymptomatic mutation carriers exhibiting normal cortical function (Geevasinga Nimeshan et al., 2015, Vucic et al., 2008). As with sporadic ALS cohorts, cortical hyperexcitability precedes the clinical development of familial ALS by months (Vucic et al., 2008). The findings from familial ALS cohorts have supported the notion that

ALS is a multistep process (Al-Chalabi et al., 2014, Vucic et al., 2020, Vucic et al., 2019), with cortical hyperexcitability being an important pathogenic step.

Reduction of LICI has been previously reported in ALS (Zanette et al., 2002a, 2002b). The reduction in LICI was accompanied by SICI reduction and correlated with greater disease severity and UMN dysfunction. Similarly, reduction of transcallosal inhibition (SIHI and LIHI) has been reported in ALS and correlated with a faster rate of disease progression and greater degree of muscle weakness (van den Bos et al., 2021). Degeneration of long-latency inhibitory circuits, acting via $GBAB_B$ receptors (Ziemann et al., 2015), was postulated to underlie these abnormalities in ALS.

Single-pulse TMS has provided additional evidence for the pathogenic importance of cortical hyperexcitability in ALS (van den Bos et al., 2019, Vucic et al., 2018). The cortical silent period was shown to be consistently reduced in ALS (Geevasinga Nimeshan et al., 2015, Geevasinga N. et al., 2015, Menon et al., 2016, Mills, 2003, Triggs et al., 1999, Vucic and Kiernan, 2006, Vucic and Kiernan, 2007, 2008, Zanette et al., 2002b). The reduction in CSP duration appears more prominent in early disease stages and is specific for ALS compared to other neuromuscular diseases (Menon et al., 2015, Vucic et al., 2011b, Vucic and Kiernan, 2008, Vucic et al., 2010). Moreover, reduction of RMTs has been reported as an early feature of ALS (Eisen and Weber, 2001, Mills and Nithi, 1997a) and associated with profuse fasciculations, preserved muscle bulk and hyperreflexia. Resting motor threshold increases with disease progression, potentially reflecting underlying UMN degeneration (Mills and Nithi, 1997a). The reduction in RMT is not an invariable finding, with some studies reporting a normal (Menon et al., 2017, Mills and Nithi, 1997a, Vucic and Kiernan, 2006, Zanette et al., 2002b), or even increased RMT (Berardelli et al., 1991, Eisen et al., 1990, Miscio et al., 1999, Triggs et al., 1999, Urban et al., 2001), reflecting clinical heterogeneity of ALS. Of relevance, TMS studies using neuronavigation have reported an increase in RMT, with a reduction in the mean motor cortical map area which could be used as a biomarker of upper motor neuron dysfunction (Chervyakov et al., 2015).

An increase in MEP amplitude has also been reported as an early feature of ALS and correlating with LMN dysfunction (Menon et al., 2015, Menon et al., 2014, Vucic and Kiernan, 2006, Vucic and Kiernan, 2007). The increase in MEP amplitude is likely to reflect enhanced corticomotoneuronal glutamatergic activity and provides further support for the pathogenic importance of cortical hyperexcitability in ALS.

The diagnosis of ALS relies on identifying concomitant upper and lower motor neuron signs in one or more body regions, with evidence of rapid disease progression (Shefner et al., 2020). Given the absence of a pathognomonic test, clinically based and consensus driven diagnostic criteria have been developed for ALS (Brooks, 1994, Brooks et al., 2000, de Carvalho et al., 2008, Shefner et al., 2020). Limitations in eliciting UMN signs in ALS, in part due to superimposed LMN dysfunction, has been well documented (Swash, 2012), and impacts on the sensitivity of the ALS diagnostic criteria (Costa et al., 2012, Geevasinga Nimeshan et al., 2016, Geevasinga N. et al., 2016b, Higashihara et al., 2012, Turner et al., 2009).

Threshold tracking TMS has proven to be a robust and objective biomarker of UMN dysfunction in ALS (Menon et al., 2015, Vucic et al., 2011b). Specifically, the presence of cortical dysfunction, as heralded by reduction of SICI or motor cortex inexcitability, reliably differentiates ALS from neuromuscular mimicking disorders, hastening the diagnosis of ALS by $\sim$ 8 months when compared to clinical criteria (Vucic et al., 2011b). Importantly, identification of cortical dysfunction enhances the diagnostic utility of the Awaji criteria by 34% irrespective of site of onset or disease stage (Menon et al., 2015). Additionally, sub-clinical identification of UMN dysfunction has further aided the diagnosis of ALS (Menon et al., 2016, Vucic and Kiernan, 2007). Separately, prolonged CMCT has also been reported as a potential diagnostic biomarker of UMN dysfunction (Eisen et al., 1990, Mills, 2003, Tokimura et al., 2020), although the sensitivity appears to be poor (Menon et al., 2015). While the main limitation of threshold tracking TMS was broader availability, the recent commercialization of the technique will likely lead to translation of threshold tracking TMS into clinical practice and therapeutic trial setting.

The PSTH technique has also disclosed abnormalities in ALS, characterised by increased dispersion and/or desynchronization of the PP (Kohara et al., 1996b, Mills, 1995, Nakajima et al., 1997). Specifically, small amplitude, delayed and desynchronized PPs, along with longer excitatory postsynaptic potential (EPSP) rise times of reduced amplitude, have been reported in ALS (Awiszus and Feistner, 1993, Eisen et al., 1996, Mills, 1995). Degeneration of fast-conducting with relative preservation of slow conducting motor pathways probably account for these findings (Eisen et al., 1996). An increase in EPSP amplitude was reported in a proportion of ALS patients (Eisen et al., 1996), potentially reflecting glutamate excitotoxicity. A limited number of longitudinal studies in ALS have suggested progression of PP abnormalities, characterised by increasing desynchronization (double peaks) and delay of PP (Weber et al., 2000). The second component of the PP probably reflect activation of higher threshold slow-conducting pathways, that could be explained by development of cortical hyperexcitability.

Abnormalities of PSTH have also been reported in multiple sclerosis and stroke (Boniface et al., 1991, Kohara et al., 1996a), although the presence of double PPs are typically evident in ALS (Weber and Eisen, 2000, Weber et al., 2009), suggesting potential diagnostic utility. While PSTH is a sensitive method for detecting UMN dysfunction (Weber and Eisen, 1999, 2000), the technique is complex, not readily applicable in clinical practice and sensitivity to detect subclinical UMN dysfunction remains to be determined.

3.1.2. Dementia

3.1.2.1. *Alzheimer's disease* (AD) is the leading cause of dementia (Gustavsson et al., 2022, Scheltens et al., 2021), clinically, characterized by amnestic cognitive impairment and dysfunction in other cognitive domains that interfere with activities of daily living (Knopman et al., 2021). Pathologically, AD is characterized by the accumulation of amyloid-β plaques and tau neurofibrillary tangles, and macroscopically by atrophy beginning in the entorhinal cortex, which spreads to the limbic and paralimbic regions, and ultimately neocortical associative areas (Frisoni et al., 2010). Although the neocortex becomes affected in more advanced stages of the disease, deficits in functional connectivity have been observed in early disease stages (Brier et al., 2012; Dennis and Thompson, 2014; Ferreri et al., 2003). Thus, TMS may represent a useful tool for *in vivo* functional evaluation of cortical networks in AD [see review (Di Lazzaro et al., 2021)].

Motor cortex excitability is increased in AD as revealed by reduction of RMT (Alagona et al., 2004, Brem et al., 2013, de Carvalho et al., 1997, Di Lazzaro et al., 2004, Di Lazzaro et al., 2008, Di Lorenzo et al., 2013, Ferreri et al., 2011, Hoeppner et al., 2012, Inghilleri et al., 2006, Issac et al., 2013, Khedr et al., 2011, Martorana et al., 2009, Martorana et al., 2008, Motta et al., 2018, Schirinzi et al., 2018, Terranova et al., 2013, Trebbastoni et al., 2012, Wang et al., 2016) and AMT (Di Lazzaro et al., 2007b, Khedr et al., 2011, Pepin et al., 1999, Wegrzyn et al., 2013).

The increase in motor cortex excitability reflects functional changes in cortical neurotransmission involving the intricate relationships between GABAergic, glutamatergic, and cholinergic neurotransmission in M1 and resulting in an imbalance between

excitatory and inhibitory activities (Di Lazzaro et al., 2004). Given that TMS produces high frequency repetitive discharge of pyramidal neurons and non-NMDA receptors are more involved in high frequency discharge, it has been suggested that enhanced excitability in AD represents enhanced neurotransmission via the non-NMDA receptors (Brem et al., 2013, Di Lazzaro et al., 2004).

Synaptic $GABA_A$ activity, as reflected by SICI, was reported to be unchanged in AD by some (Alberici et al., 2008, Benussi et al., 2018a, Benussi et al., 2018b, Benussi et al., 2017, Di Lazzaro et al., 2004, Di Lazzaro et al., 2002c, Di Lazzaro et al., 2008, Di Lazzaro et al., 2007b, Di Lorenzo et al., 2013, Martorana et al., 2013, Motta et al., 2018, Nardone et al., 2008, Olazarán et al., 2013, Pepin et al., 1999), although a reduction in SICI has also been reported (Hoeppner et al., 2012, Liepert et al., 2001, Martorana et al., 2008, Nardone et al., 2006, Olazarán et al., 2010, Pierantozzi et al., 2004b). A recent meta-analysis reported that SICI is reduced only in AD patients with longer symptom duration (Mimura et al., 2021), and it can be speculated that SICI impairment manifests only in advanced stages of AD, and that the discordant findings may be related to the varied patient characteristics across different studies.

Additionally, $GABA_B$ inhibitory neurotransmission as evaluated by CSP duration, was reported to be unchanged in most studies (Alagona et al., 2004, Di Lazzaro et al., 2002c, Inghilleri et al., 2006, Issac et al., 2013, Liepert et al., 2001, Trebbastoni et al., 2012). In contrast, reduction of LICI, another measure of $GABA_B$ neurotransmission, has been reported in a few studies (Benussi et al., 2017, Benussi et al., 2020c, Brem et al., 2013). Further studies are needed to confirm this finding. Separately, intracortical excitability as probed by ICF, tends to be reduced in AD (Alberici et al., 2008, Benussi et al., 2018b, Benussi et al., 2017, Benussi et al., 2020c, Di Lorenzo et al., 2013, Liepert et al., 2001, Martorana et al., 2013, Motta et al., 2018, Nardone et al., 2008, Nardone et al., 2006, Olazarán et al., 2010). Cholinergic-mediated inhibition evaluated with SAI was significantly decreased in AD (Bella et al., 2016, Benussi et al., 2021a, Benussi et al., 2022, Benussi et al., 2018b, Benussi et al., 2017, Benussi et al., 2020c, Di Lorenzo et al., 2013, Di Lorenzo et al., 2019, Hwang et al., 2018, Koch et al., 2016, Motta et al., 2018, Nardone et al., 2014, Schirinzi et al., 2018, Yildiz et al., 2018).

Treatment of AD patients with acetylcholinesterase inhibitors (Di Lazzaro et al., 2004), L-dopa (Martorana et al., 2009, Nardone et al., 2014) and dopamine agonists (Koch et al., 2014a, Martorana et al., 2013), was reported to normalize SAI. Interhemispheric connectivity, as assessed by interhemispheric silent period (iSP), was abnormal in AD patients as disclosed by prolonged latencies (Hoeppner et al., 2012, Khedr et al., 2011, Wegrzyn et al., 2013). Parietal-to-motor (PPC-M1) connectivity was also shown to be impaired in AD (Bonnì et al., 2013).

TMS related techniques have been successfully applied in the differential diagnosis of AD from other neurodegenerative disorders [see review (Di Lazzaro et al., 2021)]. Considering that the abnormality of single TMS measures, such as motor threshold, is not specific to AD as it has been observed in different neurodegenerative disorders such as ALS (Vucic et al., 2013b), researchers have investigated whether combined measures evaluating multiple parameters and thus multiple neurotransmitter circuits may be of greater diagnostic utility. In an early multicenter study [175 participants], using a complex parameter combining SICI, ICF and SAI measures, it was shown that TMS can differentiate AD from frontotemporal dementia (FTD) and healthy controls with a high sensitivity and specificity (Benussi et al., 2017). These initial findings were confirmed in larger study (N = 694) implementing a machine learning algorithm approach based on TMS measures (SICI, ICF, SAI and LICI), that accurately distinguished AD form other neurodegenerative disorders with a high diagnostic accuracy ranging from 89 to 92% (Benussi et al., 2020c).

3.1.2.2. *Frontotemporal dementia (FTD)* is one of the most frequent neurodegenerative dementing disorders after AD and is characterized by behavioral abnormalities, language impairment, and deficits of executive functions (The Lund and Manchester Groups, 1994). Three different variants have been proposed according to the clinical presentation: (i) behavioral variant of FTD (bvFTD) (Rascovsky et al., 2011), (ii) agrammatic variant of primary progressive aphasia (avPPA) and (iii) semantic variant of PPA (svPPA) (Gorno-Tempini et al., 2011). In approximately 10–30% cases, a genetic mutation may be found in the *microtubule associated protein tau* (*MAPT*) or *granulin* (*GRN*) gene, or expansion on *chromosome 9 open reading frame 72* (*C9orf72*) (Benussi et al., 2021c).

Several motor circuit abnormalities have been reported in FTD, including reduction in M1 excitability or absent MEPs, increase in MEP latencies and CMCT (Bae et al., 2016, Burrell et al., 2011, Chandra et al., 2016, Di Lazzaro et al., 2006a, Wang et al., 2016). SICI and ICF are significantly reduced in FTD (Bae et al., 2016, Benussi et al., 2018a, Benussi et al., 2021a, Benussi et al., 2020a, Benussi et al., 2020b, Benussi et al., 2020c, Benussi et al., 2020d, Burrell et al., 2011, Di Lazzaro et al., 2006a, Padovani et al., 2018, Palese et al., 2020), mirroring the GABAergic and glutamatergic abnormalities which are characteristic of FTLD pathology (Benussi et al., 2019a, Murley and Rowe, 2018). Normal level of SAI was demonstrated by many studies (Benussi et al., 2018a, Benussi et al., 2016, Benussi et al., 2020b, Benussi et al., 2017, Benussi et al., 2019c, Di Lazzaro et al., 2006a, Padovani et al., 2019), confirming that cholinergic deficits are not evident in FTD.

3.1.2.3. *Mild cognitive impairment* (MCI) is an intermediate condition between normal aging and dementia. Approximately 50% of patients diagnosed with mild cognitive impairment progress to dementia within 3 to 5 years of diagnosis (Albert et al., 2011, Petersen et al., 2014), underscoring the importance of effective diagnostic biomarkers at a potentially early stage of the disease (Rossini et al., 2022). Of relevance, 70–80% of patients with amnestic mild cognitive impairment have associated AD pathological changes, while 20–30% have other neuropathological processes, including frontotemporal lobar degeneration, Lewy body disease or vascular changes (Petersen and Negash, 2008). Clinical and pathological heterogeneity in mild cognitive impairment could explain the contrasting TMS findings.

In some studies, a non-significant increase in M1 excitability was reported, like that reported in AD (Benussi et al., 2021b, Nardone et al., 2012, Olazarán et al., 2010, Padovani et al., 2018, Sakuma et al., 2007, Tsutsumi et al., 2012). In contrast, no significant differences in SICI and ICF were evident in mild cognitive impairment (Benussi et al., 2021b, Nardone et al., 2012, Olazarán et al., 2010, Padovani et al., 2018, Tsutsumi et al., 2012). Most studies have reported a decrease in SAI (Benussi et al., 2017, Benussi et al., 2021b, Benussi et al., 2020c, Padovani et al., 2018, Peter et al., 2016, Tsutsumi et al., 2012), with one study reporting reduction in amnestic mild cognitive impairment patients only (Nardone et al., 2012), while another study did not show any abnormalities (Sakuma et al., 2007). LTP-like plasticity was found to be unaltered in mild cognitive impairment (Lahr et al., 2016).

A single center study reported high diagnostic accuracy (~90%) of TMS in diagnosing mild cognitive impairment related to AD when compared to non-AD related mild cognitive impairment (Padovani et al., 2018). Specifically, a novel index encompassing SICI, ICF and SAI *([SICI-ICF]/SAI)* differentiated AD from non-AD mild cognitive impairment with a specificity of 87.9% and sensitivity of 94.4%. The utility of the novel TMS index was comparable to established biomarkers of amyloidosis (Padovani et al., 2019). A recent multicenter study, utilizing a machine learning algorithm

approach re-affirmed a high accuracy [72 to 86%], precision [72–90%] and recall [75–98%] of TMS (SICI, ICF, SAI and LICI measures) in classifying different mild cognitive impairment phenotypes (Benussi et al., 2021b).

3.2. Movement disorders

Over the years, there has been increased interest in investigating changes of motor cortex in patients with movement disorders, particularly Parkinson's disease (PD) and dystonia with TMS studies. Motor cortex has also been investigated in other types of movement disorders, including atypical parkinsonism, tic, and Tourette's syndrome (TS), as well as Huntington's disease (Bologna et al., 2022).

3.2.1. *Parkinson's disease* (PD): Parkinson's disease is a common movement disorder affecting 1% of the population aged > 65 years, clinically presenting with rest tremor, bradykinesia, and rigidity (Bloem et al., 2021). In PD patients, RMT and AMT were normal in most studies (Chen and Rothwell, 2012), although some studies reported a reduction of RMT (Tremblay and Tremblay, 2002, Valls-Sole et al., 1994), more prominent on the side exhibiting greater rigidity (Cantello et al., 1991, Spagnolo et al., 2013). Increased AMT may correlate with bradykinesia in PD patients, which could be related to difficulties in volitional contraction (Ellaway et al., 1995), although another study did not reveal the same findings (Bologna et al., 2018). In fact, a recent study showed that PD patients with tremor-dominant subtype had both RMT and AMT reduction compared to controls and akinetic-rigid patients (Khedr et al., 2021). The MEP amplitude and the IO curve steepness were found to be increased at rest but reduced with muscle contraction in PD (Valls-Sole et al., 1994). The slope of the IO curve correlated with disease stage and severity of bradykinesia (Bologna et al., 2018, Valls-Sole et al., 1994). A compensatory increase in cortical excitability in response to bradykinesia may account for these TMS findings.

Reduced SICI (Ni et al., 2013, Ridding et al., 1995) and CSP duration (Cantello et al., 2002) have been reported in PD, indicated dysfunction of GABAergic circuits, although at least one paper reported normal SICI in PD, albeit with anterior-posterior directed currents (Hanajima et al., 2011). The degree of reduction of SICI was similar across levodopa-naïve, non-dyskinetic and dyskinetic patients (Ammann et al., 2020). Importantly, SICI was also reduced on the less affected side, even in drug-naïve patients in whom the less affected side was minimally symptomatic (Ammann et al., 2020). With disease progression, there is a further reduction in SICI (Kojovic et al., 2015). Normalization of SICI has been reported with dopaminergic medications (Ni et al., 2013, Ridding et al., 1995) and subthalamic nucleus deep brain stimulation (Cunic et al., 2002), although others have not reported any modulating effects of dopaminergic medications on SICI (Bologna et al., 2018, Lewis and Byblow, 2002, MacKinnon et al., 2005). The discordant findings may be related to heterogeneity of PD patients across different studies. Reduced LICI at ISIs 100 to 150 ms was also reported in PD patients at rest (Chu et al., 2009), although normal or increased LICI have also been reported in PD (Sailer et al., 2003, Valzania et al., 1997). Increased LICI (at ISIs 150–200 ms) with minimal muscle contraction was also reported in PD (Berardelli et al., 1996). The variable LICI findings could be related to different measurement conditions such as conditioning stimulus intensity, ISI, or target muscle status (rest or active). Of further relevance, a significant reduction of CSP duration has been reported in PD patients that were in the "OFF" compared to "ON" state, although in both states the CSP duration was not significantly different when compared to healthy controls (Ridding et al., 1995). Consequently, monitoring CSP duration could serve as a therapeutic biomarker in PD.

Normal (Ridding et al., 1995) or reduced ICF (Bares et al., 2003) has been reported in PD patients (Lefaucheur et al., 2004), while SICF is increased and was associated with reduced SICI, suggesting that SICF could partially account for decreased SICI (Ni et al., 2013). The increase in SICF was observed in de novo PD patients (Shirota et al., 2019) and is further enhanced in PD patients with dyskinesia (Guerra et al., 2019). A triple-pulse protocol reported that in the presence of SICI, SICF-1 was further facilitated in normal subjects but not in PD patients, especially in patients with greater motor impairment, and the effect may be normalized by levodopa (Saravanamuttu et al., 2021). In another study, the combined effect of SICI and SICF-1 (ISI 1.5 ms) was comparable between drug naïve PD patients and healthy controls (Shirota et al., 2019). These findings suggest that abnormal interactions between cortical circuits may be a feature of PD, and the effects may depend on disease stage.

The function of the corpus callosum is affected in PD patients. Specifically, while LIHI was reduced in PD patients with mirror movements, SIHI was normal (Li et al., 2007). Additionally, patients with tremor-dominant subtype were shown to have shorter iSP duration compared to akinetic-rigid patients, while iSP latency tended to be longer in akinetic-rigid patients compared to healthy controls (Khedr et al., 2021).

SAI was reported to be either normal or increased in PD patients off dopaminergic medications (Nardone et al., 2005), but reduced in those taking dopamine medications (Sailer et al., 2003). Stronger SAI was associated with higher gait speed and longer step length in patients receiving dopaminergic medications (Rochester et al., 2012), with SAI partially explaining the variability of gait speed (Rochester et al., 2012). Reduction of SAI was also evident in PD patients prone to falling, even after adjusting for cognitive function (Pelosin et al., 2016), suggesting a role for SAI as a predictive biomarker for gait, posture, and balance impairment. Separately, cognitive impairment in PD was also associated with reduced SAI (Celebi et al., 2012, Nardone et al., 2013a, Yarnall et al., 2013). Reduction of LAI was also reported in PD and was independent of medication states (Sailer et al., 2003). Impairment of the cerebellar-M1 connections, as reflected by reduced CBI, was reported in PD patients off medications which normalized with dopaminergic treatment (Ni et al., 2010, Shirota et al., 2010), although others have reported CBI reduction irrespective of treatment status (Carrillo et al., 2013).

3.2.2. *Atypical Parkinsonism*: Atypical Parkinsonian syndromes includes multiple systemic atrophy (MSA), progressive supranuclear palsy (PSP) and diffuse Lewy body dementia. Atypical parkinsonism may be with similar clinical presentation to Parkinson's disease, but some electrophysiological responses are different between each disorder. Several subtypes of PSP have been described and most studies focused on the typical Richardson subtype. PSP patients exhibit normal CMCT in early disease (Fisicaro et al., 2020), with evidence of CMCT prolongation with disease progression that correlates with disease duration (Abbruzzese et al., 1991, Morita et al., 2008). Moreover, PSP patients exhibit reduced SICI and steeper IO gradients at rest (Conte et al., 2012), as well as normal ICF (Bologna et al., 2017, Kuhn et al., 2004). Reduced iSP duration, implying transcallosal dysfunction, has been reported in the Richardson but not in the Parkinson subtype of PSP (Wittstock et al., 2013). SAI is unchanged in PSP, irrespective of cognitive function, suggesting that cognitive dysfunction evident in PSP is unrelated to deficits in cholinergic pathways (Nardone et al., 2005). Additionally, decreased CBI indicates involvement of the dentate-thalamo-cortical pathway in PSP (Brusa et al., 2014, Shirota et al., 2010), which is compatible with pathological findings showing dentate nucleus and superior cerebellar peduncle degeneration in PSP (Kanazawa et al., 2009).

Several studies showed prolonged CMCT in MSA (Eusebio et al., 2007, Morita et al., 2008), which may be related to UMN signs. Paired-pulse studies showed reduced SICI but normal ICF (Marchese et al., 2000, Suppa et al., 2014). Normal SICF at ISI of 3 ms was reported in both MSA parkinsonism and cerebellar (MSA-C) subtypes (Suppa et al., 2014), suggesting diagnostic utility in differentiating MSA form PD (Ni et al., 2013, Shirota et al., 2019). Prolonged contralateral and ipsilateral CSP durations were reported in MSA (Kuhn et al., 2004), although others found no significant changes (Wolters et al., 2004). Reduced SAI, elicited with digit stimulation, was reported in MSA patients, implying abnormalities in central cholinergic or GABAergic pathways (Mascia et al., 2005). SAI evoked by median nerve stimulation was reduced in MSA-C with cognitive dysfunction, as was CBI which correlated with ataxia severity (Shirota et al., 2022).

Diffuse Lewy body dementia (DLBD) manifests as parkinsonism and dementia, frequently accompanied by cognitive fluctuation, executive or visuospatial dysfunction and rapid eye movement (REM) sleep behavioral disorder (McKeith et al., 2017). In DLBD, reduction of SAI has been reported (Di Lazzaro et al., 2007b, Marra et al., 2012), and a greater SAI reduction was associated with visual hallucinations (Marra et al., 2012), implying central cholinergic deficits (Marra et al., 2012, Tiraboschi et al., 2000). More recent studies have confirmed previous findings of reduced SAI in larger cohorts, at ISIs of N20 + 0 ms and N20 + 4 ms, which may be useful to distinguish atypical parkinsonian syndrome from DLBD (Benussi et al., 2018b, Benussi et al., 2020c). The reduction in SAI, however, is not an invariable finding (Nardone et al., 2006), and larger studies with pathological confirmation used as a reference standard for DLBD diagnosis may be required to confirm a potential diagnostic utility of SAI in DLBD.

3.2.3. *Huntington's disease*: In Huntington's disease (HD), discordant single and paired pulse TMS findings have been reported. While some studies disclosed increased RMT (Schippling et al., 2009), others have reported normal RMT values (Kamble et al., 2018). Similarly, CSP duration was reported to be either normal or reduced (Schippling et al., 2009, Tegenthoff et al., 1996). While the discordant findings were related to phenotypic heterogeneity and differences in methodology (Berardelli et al., 1999, Modugno et al., 2001, Wassermann et al., 2008), CSP shortening correlated with functional decline in HD (Lefaucheur et al., 2006b). Additionally, while some studies reported normal SICI (Hanajima et al., 1999, Priori et al., 2000), other have documented reduced SICI (Abbruzzese et al., 1997, Kamble et al., 2018) and increased ICF (Abbruzzese et al., 1997, Nardone et al., 2007), suggesting abnormalities of intracortical glutamatergic pathways. Reduced SAI was reported in HD gene carriers and early-stage HD patients, suggesting impairment of sensorimotor integration in the presymptomatic or early stages of disease. Greater reduction in SAI correlated with an earlier age of disease onset and more severe phenotype (Schippling et al., 2009).

3.2.4. *Dystonia*: Dystonia is characterized by involuntary muscle contraction that elicits abnormal posture or irregular repetitive movements. Agonist and antagonist muscle co-contraction is typically recorded. TMS studies in dystonia have revealed normal RMT and IO curves (Kojovic et al., 2013, Quartarone et al., 2009), while most have reported reduced SICI, CSP duration and absence of ICF (Espay et al., 2006, Ridding et al., 1995). Reduced SICI may be evident in idiopathic dystonia (Gilio et al., 2003), dopa-responsive dystonia (Huang et al., 2006) or asymptomatic carriers of the dystonia-1 (DYT-1) gene mutations (Edwards et al., 2003), suggesting dysfunction of cortical inhibitory circuits. In contrast, some studies have reported increased ICF and normal SICI in cervical (Amadio et al., 2014, Ganos et al., 2018a) and focal hand dystonia (Rona et al., 1998) as well as Segawa disease (DYT5) (Hanajima et al., 2007). Differences in dystonic location does not account for TMS differences since reduced SICI was also evident in cervical dystonia when assessed from the unaffected limb (Kanovský et al., 2003). Botulinum toxin treatment could potentially account for the discordant findings (Amadio et al., 2014), since botulinum toxin may restore abnormal SICI one month after injection (Gilio et al., 2000). Methodological differences and individual variability could also contribute to discordant findings (Hanajima et al., 2008).

Separately, reduced resting LICI may be observed in the affected hemisphere in writer's cramp (Espay et al., 2006), whereas active LICI may be normal (Espay et al., 2006), decreased (Chen R et al., 1997) or increased in dystonia (Rona et al., 1998). CSP duration may be reduced (Chen R et al., 1997), although the results seem task dependent with CSP duration reduced during pincer grasp but normal when performing full strength grip (Stinear and Byblow, 2005, Tinazzi et al., 2005). Prolonged iSP was reported in writer's cramp, reflecting increased activation of transcallosal projections from the stimulated motor cortex to inhibitory interneurons in the non-stimulated contralateral motor cortex (Niehaus et al., 2001).

Assessment of transcallosal inhibitory connections have disclosed variable findings, depending on presence of mirror movements or whether dystonia is sporadic or familial. Reduced SIHI and LIHI in the affected but not unaffected hand was reported in focal hand dystonia (Nelson et al., 2010), being most prominent at beginning of movement and associated with mirror dystonia (Beck et al., 2009). Others have reported a reduction of SIHI and LIHI in both the affected and unaffected hands in writer's cramp patients with mirror dystonia, and a greater decrease in IHI was evident with more severe dystonia (Sattler et al., 2014). In musician's dystonia, IHI impairment may be an endophenotypic biomarker as its reduced in asymptomatic first-degree family members (Bäumer et al., 2016). Surround inhibition is considered a cortical physiological function that suppresses an area surrounding activated neural circuits to enable recruitment of a specific neuronal population. Dystonia patients exhibit decreased surround inhibition (Beck et al., 2008, Sohn and Hallett, 2004).

Sensory-motor integration appears to be abnormal in dystonia. LAI, generated by mixed nerve stimulation at ISI of 200 ms, reversed to facilitation in focal hand dystonia but not in cervical dystonia patients (Abbruzzese et al., 2001), and was most prominent during initiation of a phasic movement. Consequently, decreased LAI cannot explain involuntary contractions or reduced surround inhibition in dystonia patients (Pirio Richardson et al., 2009). Discordant findings have been reported for SAI in dystonia, which represent sensory-motor integration mediated by cholinergic and GABAergic pathways. With digit stimulation, reduced SAI with topographical suppression has been reported in focal hand dystonia (McDonnell et al., 2007), and only in tested muscle located near the digit that was stimulated. When SAI was tested with median nerve stimulation, facilitation was observed at ISIs of N20 + 10 ms (Kessler et al., 2005), but was normal at other ISIs (25 ms) (Quartarone et al., 2009).

Reduced CBI was also reported in focal hand dystonia (Brighina et al., 2009b), suggesting a pathophysiological role for cerebello-thalamo-basal ganglia pathway (Kaji et al., 2018). In contrast, CBI was reported to be normal in cervical dystonia (Koch et al., 2014b), suggesting differences in pathophysiology across the dystonic phenotypes. Additionally, the suppression of SICI and enhancement of ICF with cerebellar stimulation evident in healthy controls was absent in dystonia patients (Brighina et al., 2009b). Additionally, CBI reduction was documented in focal upper limb dystonia (Brighina et al., 2009b), but not cervical dystonia (Sondergaard et al., 2021b), although the severity of cervical dystonia significantly correlated with CBI reduction (at ISI 5 ms) implying a pathophysiological role for cerebello-thalamo-cortical tract dysfunction in focal dystonias. It should be stressed that assess-

ment of cortical inhibition cannot distinguish organic from functional dystonia's since CSP duration, SICI and LICI are all reduced in the latter (Avanzino et al., 2008, Espay et al., 2006). SICI and CSP duration in fixed dystonia's, considered a subtype of functional dystonia, were also reduced.

3.2.5. *Tics and Tourette's syndrome*: Patients with tics and TS have normal RMT and IO curves (Heise et al., 2010, Orth et al., 2008). In Tourette's syndrome, motor cortex excitability was reduced in the period immediately preceding voluntary movement and during tic suppression (Draper et al., 2015, Ganos et al., 2018b, Jackson et al., 2013). Paired pulse TMS studies have demonstrated SICI reduction in Tourette's syndrome which correlates with motor tic severity (Gilbert et al., 2004, Orth et al., 2008, Orth and Rothwell, 2009, Ziemann et al., 1997a). CSP duration in Tourette's syndrome patients was significantly reduced compared to controls (Ziemann et al., 1997a).

3.3. Myelopathy and spinal cord injuries

3.3.1. *Cervical spondylitic myelopathy:* In chronic spondylitic myelopathy, the CMCT remains the most robust and commonly utilized parameter for evaluating the damage to the corticospinal tract due to spinal cord compression (Funaba et al., 2015, Lo, 2007, 2008). By evaluating CMCT for both proximal and distal upper limb muscles it is also possible to identify more precisely the level of cord dysfunction (Di Lazzaro et al., 1992). CMCT may be abnormal even in the absence of pyramidal signs (Lanza et al., 2020), and is particularly sensitive when MEPs were obtained from the abductor pollicis brevis (APB) muscle, at least for C6-C7 myelopathy (Imajo et al., 2018, Shibuya et al., 2014). The prolongation in CMCT has also been correlated with the ratio of flattening and anteroposterior diameter parameters visualized with MRI (Rikita et al., 2017) and kinematic CT myelography (Funaba et al., 2021), as well as long-term functional outcome after cervical spine decompression (Deftereos et al., 2015, Mazur et al., 2014, Nakanishi et al., 2014, Takahashi et al., 2008). Abnormal CMCT was also documented in other myelopathies, including those resulting from high voltage electrical burns, even if MRI was unremarkable (Seo et al., 2011), and mucopolysaccharidosis (Cantone et al., 2019).

Chronic spondylitic myelopathy exhibits similar features as chronic progressive spinal cord injury and may share similar TMS findings. Specifically, motor cortex mapping with TMS showed dynamic changes after chronic spondylitic myelopathy surgery (Green et al., 2015) and spinal cord injury (Tazoe and Perez, 2021). The findings pertaining to CSP duration have been more variable, including an increase (Barry et al., 2013), reduction (Shimizu et al., 2000) or absence of change (Nardone et al., 2013b).

3.3.2. *Spinal cord injuries:* In spinal cord injuries, TMS assesses the functional integrity of the corticospinal tracts and motor control mechanisms. While no single TMS parameter may be considered a validated biomarker here, it may provide additional information on severity, prognosis and therapy. TMS provides information in four domains: assessment of residual function, cortical excitability changes, longitudinal follow up, and rehabilitation. TMS provides a useful method of assessing abdominal muscle motor preservation in spinal cord injury (Bjerkefors et al., 2015), as demonstrated in residual innervation of pelvic floor muscles by indirect cortical descending pathways (Williams et al., 2020). Additionally, TMS studies have disclosed preservation of crossed corticospinal facilitation in truncal muscles after an incomplete spinal cord injuries, as reflected in truncal control during functional arm movements (Chiou and Strutton, 2020). Another study suggested that paired corticospinal-motoneuronal stimulation may enhance spinal plasticity after spinal cord injury (Bunday et al., 2018).

Deafferentation due to acute spinal cord injuries can change the state of large cortical networks within one hour, and these changes play a critical role in the functional reorganization of central pathways (Nardone et al., 2013c). With chronic cervical spinal cord injuries, individuals have lower MEP amplitudes and a tendency toward higher TMS motor thresholds relative to healthy controls. However, no significant difference in CSP duration was observed (Sfreddo et al., 2021). A study on cortical stimulation had found prolonged MEP latencies in all coil orientations in spinal cord injuries compared to control subjects. However, the MEP latencies elicited by posterior-anterior and anterior-posterior compared to lateral-medial cortical stimulations were shorter in spinal cord injuries, particularly for MEPs elicited by anterior-posterior currents (Jo et al., 2021). MEP amplitudes remained unchanged in muscles at and within 5 segments below the cord injury during 70% of maximum voluntary contraction compared to rest. In muscles beyond the 5 segments below spinal cord injuries, MEP amplitudes were significantly higher (Bunday et al., 2013).

Paired pulse TMS studies have reported increased SICF in spinal cord injuries patients with normal CMCT, while those with abnormal CMCT showed lower SICF. The neural elements producing SICF could have increased in activity after spinal cord injuries to enhance activation of residual corticospinal tract pathways, compensating for impairment of the motor cortex in generating appropriate voluntary movements (Nardone et al., 2015a, Nardone et al., 2015b). Incomplete spinal cord injuries reduces SICI compared to controls (Roy et al., 2011), suggesting an increase in cortical excitability. In contrast, other studies have reported increased AMTs and CSP duration with spinal cord injuries (Freund et al., 2011), suggesting reduced cortical excitability. The discordant cortical excitability findings in spinal cord injuries may be related to small study cohorts and require further validation in larger sample of subjects (Nardone et al., 2015b). More recent studies have suggested that deficits in corticospinal transmission after incomplete cervical spinal cord injuries extend to the preparatory phase of upcoming movements (Federico and Perez, 2017).

Smaller MEP amplitudes and a shortening of reaction time to startle have been reported in patients with incomplete spinal cord injuries and spasticity, suggesting that imbalanced corticospinal and reticulospinal tract contributions are more pronounced in participants with chronic incomplete spinal cord injuries (Sangari and Perez, 2019). Increased reticulospinal inputs to biceps but not triceps brachii, and loss of corticospinal drive to triceps brachii in tetraplegic spinal cord injuries patients likely represent reorganization of descending motor control, thereby contributing to asymmetrical recovery between elbow flexor and extensor muscles after cervical spinal cord injuries I (Sangari and Perez, 2020). Overall, lesion studies involving corticospinal and vestibulospinal pathways, which makes differential contributions to impairment of gait ability and balance, indicate that no single electrophysiological or anatomical measure can provide an optimal prediction of clinical gait and balance disability as an ideal biomarker in spinal cord injuries (Barthélemy et al., 2015).

A long-term study of spinal cord injuries patients revealed a significant decrease in motor cortical excitability acutely, involving spinal segments below the lesion and sparing muscles rostral to the lesion, with the inhibition persisting for up to 3 years (Kriz et al., 2012). Another study reported an increase in MEP amplitude over a 12-month follow-up period which was paralleled by a significant improvement of motor and walking function (Petersen et al., 2012). Rapid motor cortical reorganization was demonstrated after spinal cord injuries which normalized at 24 months post injury (Dias Leao et al., 2020, Fassett et al., 2018). Motor maps areas are also increased when assessed at rest and decreased during voluntary contraction, with reduction being greater in patients with greater sensory deficits (Tazoe and Perez, 2021). These find-

ings suggest that sensory input may further reshape abnormal changes in motor cortical maps in humans with chronic spinal cord injuries during voluntary contraction. Additionally, MEPs can be recorded from bulbocavernosus and external anal sphincter muscles with cortical and sacral nerve root stimulation, to assess peripheral innervation and central motor control in sacral/pudendal territories and to demonstrate the presence of neurological disorder affecting the genito-urinary tracts (Opsomer et al., 1989) or anorectal function (Lefaucheur, 2006).

3.4. Epilepsy

Cortical excitability appears to be increased in drug naïve epilepsy patients, being most prominent in generalized epilepsy. For generalized epilepsy, the majority of studies have reported lower RMTs (de Goede et al., 2016), although the reduction was only significant in specific epilepsy phenotypes including juvenile myoclonic epilepsy (Badawy et al., 2013b, Cuypers et al., 2013). Additionally, a meta-analysis reported a non-significant trend towards lower RMTs for generalized epilepsy in general, with the reduction being significant only in JME (Brigo et al., 2012). In contrast, others have reported increased RMT values, which was attributed to activation of inter-ictal compensatory mechanisms to prevent the spreading or recurrence of new seizures (Badawy et al., 2009, Lee et al., 2015) or as a result of antiepileptic drugs (AEDs) which block sodium channels (Rossini et al., 1994, Rossini et al., 2015, Ziemann et al., 2015). In focal epilepsy, RMT was not significantly different when compared to healthy controls (de Goede et al., 2016). Separately, the MEP amplitudes were within normal limits for both generalized and focal epilepsy phenotypes (de Goede et al., 2016, Klimpe et al., 2009, Lee et al., 2015).

Prolonged CSP duration has been reported in generalized epilepsy, a finding attributed to a protective hyperactivation of inhibitory circuits acting to prevent recurrence of new seizures (Cincotta et al., 2015, de Goede et al., 2016). A significant reduction in CSP duration was reported in the familial cortical myoclonic tremor with epilepsy phenotype (Suppa et al., 2009). In focal epilepsy, non-significant reduction in CSP duration has been reported (Cincotta et al., 2015, de Goede et al., 2016).

In drug naïve patient with generalized epilepsy, SICI (measured at ISI of 2 and 5 ms) was reported to be reduced or absent in the contra-and ipsilateral motor cortices (Badawy et al., 2012, 2013a, Badawy et al., 2010, Badawy et al., 2013b, de Goede et al., 2016, Werhahn et al., 2000a), although this was not a consistent finding (Cantello et al., 2006, de Goede et al., 2016, Lee et al., 2015). Although there was no significant difference in ICF measured at ISIs 10 ms and 15 ms in generalized epilepsy (Badawy et al., 2012, 2013a, Badawy et al., 2010, Badawy et al., 2013b, Lee et al., 2015), averaged ICF was increased (Cantello et al., 2006). Interestingly, ICF may be decreased within 48 hours of a grand-mal seizure (Delvaux et al., 2001). For focal epilepsy, SICI was reduced while no significant changes were evident for ICF (de Goede et al., 2016).

LICI was abnormal in generalized epilepsy, with absence of inhibition evident at ISIs of 50, 150, 250 and 300 ms (Badawy and Jackson, 2012, Badawy et al., 2012, 2013a, Badawy et al., 2010, Badawy et al., 2013b). In focal epilepsy, LICI was facilitated on the ipsilateral side at ISIs of 250 and 300 ms.

Patients with some forms of epilepsy are more likely to have seizures after sleep deprivation or when assessed in the early morning period, and these factors can increase the likelihood of detecting interictal EEG epileptiform abnormalities (Badawy et al., 2006, Renganathan and Delanty, 2003). TMS studies have shown that these activating factors are associated with increased cortical excitability and reduced intracortical inhibition, potentially accounting for an increased risk of seizures in these settings (Badawy et al., 2006, Kreuzer et al., 2011, Manganotti et al., 2006, Serafini et al., 2013).

A potential limitation of using TMS in epilepsy relates to MEP variability in patients and controls (Corp et al., 2021). While MEP variability may be reduced with close attention to target muscle, pulse waveform and use of neuronavigation, current findings can only be reliably applied in a large cohort setting and not on an individual patient. Consequently, it seems unlikely that TMS will be able to be used as a diagnostic biomarker in epilepsy. In one study using LICI, the reported diagnostic sensitivity was reported to be as low as 24% (Young et al., 2009). The utility of TMS may be in evaluating the physiological effects of AEDs as a biomarker of changes in cortical excitability and future seizure risk (Badawy et al., 2012).

3.5. Migraine and other headaches

The first ten years of this century were dedicated to exploring the pathophysiology of migraine with TMS and to examine the clinical diagnostic utility of the different TMS techniques applied on distinct brain areas (Chen et al., 2008). The studies performed have provided seemingly contradictory findings, reasonably because each investigation had depicted distinct facets of a complex pathophysiological mechanism. In the last ten-to-twelve years, although great efforts have been devoted to test TMS as a possible treatment for migraine, some of the original contradictions have been clarified, whereas others remained unsolved.

3.5.1. *Migraine without aura*: Abnormal cortical plasticity was reported in ***migraine without aura (MO)*** patients, and these plasticity changes were most evident on paired associative stimulation testing when the ISI was set to 10 ms, with MEP responses potentiated (Pierelli et al., 2013). Variability in RMT findings have been reported in MO patients, including normal, increased, or reduced RMT (Afra et al., 1998, Badawy and Jackson, 2012, Bettucci et al., 1992, Brighina et al., 2010, Cortese et al., 2017, Gunaydin et al., 2006, Maertens de Noordhout et al., 1992, Neverdahl et al., 2017, Pierelli et al., 2013, Siniatchkin et al., 2009, van der Kamp et al., 1996, van der Kamp et al., 1997, Werhahn et al., 2000b). The RMT appears to be influenced by the proximity of a migraine attack, being higher if measured closer to the attack (Cortese et al., 2017), potentially accounting for the variability of RMT findings. Dependance on the exact time-point at which physiological measurements are made during the migraine cycle was not confirmed in the motor cortex of children and adolescents but was replicated in the visual cortex (Siniatchkin et al., 2009). These findings confirm that excitability of motor and occipital cortex may differ in the same patient.

CSP duration, assessed interictally, was reported to be normal in MO patients (Maier et al., 2011, Siniatchkin et al., 2007), although was reduced in female interictal migraineur patients (Neverdahl et al., 2017, Yuksel and Topalkara, 2021). CSP shortening was exacerbated by a contingent negative variation task requiring focused sustained attention (Maier et al., 2011), and induced by sleep restriction especially in patients with non-sleep related migraine (Mykland et al., 2022).

In patients studied interictally, SICI was decreased when tested at ISI of 4-ms but not 2-ms (Cosentino et al., 2018, Mykland et al., 2022, Neverdahl et al., 2017). These observations underly the relevance of the stimulation parameters used when testing intracortical inhibition in migraine. Using standard stimulation paradigms, ICF was reported to be normal interictally (Neverdahl et al., 2017), albeit increased when using suprathreshold conditioning stimuli (Siniatchkin et al., 2007). The increase in ICF with subthreshold conditioning stimuli was only evident with low suprathreshold test stimuli [110%RMT] (Cosentino et al., 2018). During the preictal phase ICF decreased (Neverdahl et al., 2017), indicating that changes in migraine cycle affect ICF.

LICI studied with ISIs up to 120-ms showed no significant abnormality in migraine patients (Cosentino et al., 2018, Siniatchkin et al., 2007). Increasing the test stimulus intensity to 150% RMT leads to reduction of LICI, which positively correlates with disease duration (Cosentino et al., 2018). In a separate study, LICI was reduced at ISI of 250-ms (Badawy and Jackson, 2012), implying dysfunction of long latency intracortical inhibitory circuits in migraine. When studied interictally, SAI was found to be either normal (Alaydin et al., 2019) or reduced (Coppola et al., 2020) in MO patients. When assessed in the immediate preictal or ictal periods, SAI was reduced (Alaydin et al., 2019, Coppola et al., 2020).

3.5.2. *Migraine with aura:* ***In migraine with aura*** (MA) patients, TMS studies have disclosed normal RMT (Badawy and Jackson, 2012, Brighina et al., 2011, Cosentino et al., 2011), but increased MEP amplitude in response to increasing stimulus intensity (Cosentino et al., 2011) or repetitive TMS (rTMS) [at 5 Hz] delivered at 110% RMT intensity (Brighina et al., 2011). The changes in TMS variables were reversed by prophylactic levetiracetam treatment (Brighina et al., 2011, Cosentino et al., 2011). Of relevance, visual cortex exhibited reduced TMS-elicited phosphene thresholds, which was reduced by anodal transcranial direct current stimulation (Chadaide et al., 2007). Low-frequency rTMS (at 1 Hz) resulted in a reduction in TMS-elicited phosphene thresholds, an effect reverted by valproate treatment (Palermo et al., 2009).

The CSP duration was reduced in MA patients (Chen et al., 2008, Maier et al., 2011, Mykland et al., 2022), while LICI at ISI 250 ms was facilitated (Badawy and Jackson, 2012). The deficits of cortical inhibition appear to be more related to aura rather than headache mechanisms. Additionally, reduction of CSP duration was reported interictally, in females migraineurs during pre-ovulatory recordings (Yuksel and Topalkara, 2021), and may be evident when recording from facial muscles (Curra et al., 2007). Based on the calcium channel hypothesis of hemiplegic migraine and the observation that P/Q-type calcium channels are strongly expressed in the cerebellum, CBI was shown to be reduced in MA patients (Brighina et al., 2009a).

Occipital TMS may also be an effective tool in discriminating between transient ischemic attacks and migraine aura without headaches aura based both on the frequency and threshold of inducing phosphenes (Naeije et al., 2017), although further studies are required to confirm utility. Interestingly, topiramate modulates occipital cortex excitability, although the modulating effects were independent of clinical benefits, as reflected by reduction in headache frequency (Aurora et al., 2010). In chronic migraine patients without aura, RMT was reduced and SICI absent, while patients with episodic migraine exhibited normal RMT and SICI values (Valente et al., 2021). Botulinum toxin therapy resulted in partial normalisation of SICI in the chronic migraine patients after 12-months of treatment accompanied by improvement in pain (Valente et al., 2021). Taken together, it was proposed that botulinum toxin therapy resulted in long-term alteration of cortical plasticity, mainly due to effects on chronic pain.

TMS studies in episodic cluster headaches disclosed physiological RMT and CSP duration values in both hemispheres, while SICI was reduced and ICF increased in the ipsilateral hemisphere to the headache side (Cosentino et al., 2015). Of relevance, SICI was reduced when assessed ictally, whereas ICF was increased both ictally and interictally. Similarly, a reduction of SICI and increase in ICF were reported in cluster headache and allodynia (Ekizoglu et al., 2015).

In patients with medication-overuse headache, the CSP differed according to the type of medication overused (Currà et al., 2011). In patients overusing triptans alone, CSP duration was reduced, similar to migraineur patients. In contrast, overuse of non-steroidal anti-inflammatory agents alone or in combination with triptans, was not associated with abnormalities of CSP duration. The cortical changes were attributed to medication-induced neural adaptation, potentially mediated by alterations in central serotonin neurotransmission.

3.6. Neuropathic pain

In acute or tonic pain experiments, various changes in corticospinal motor excitability occur, as assessed by TMS techniques (Burns et al., 2016a, Lefaucheur, 2004). A recent meta-analysis concluded that greater reduction motor cortex excitability was associated with shorter durations and higher levels of induced experimental pain (Chowdhury et al., 2022). Additionally, corticomotor depression in the early stage of pain could indicate a higher susceptibility to development of chronic pain (Seminowicz et al., 2019). In chronic pain, measures of cortical excitability can reflect impairment of various neurotransmitter systems related to maladaptive plasticity of pain modulatory systems. Corticospinal excitability changes are not specific to pain pathophysiology. Therefore, TMS is not a relevant tool for diagnosis of chronic pain or its mechanisms (neuropathic, nociceptive, or nociplastic), but could be a biomarker to understand or monitor therapeutic analgesic interventions.

Only two meta-analyses that assessed changes of cortical excitability parameters in chronic pain have been published (Chang et al., 2018, Parker et al., 2016). A significant reduction of SICI and CSP duration was reported in one study, especially in the context of neuropathic pain (Parker et al., 2016). A trend towards increased SICF was reported, albeit from a single study, while no difference was found for RMT, IO curve, ICF, and LICI in chronic pain. A subsequent meta-analysis reported inconclusive findings regarding reduction in SICI and CSP duration, except in complex regional pain syndrome, with a trend towards increased LICI in chronic pain (Chang et al., 2018). Other reviews have also discussed cortical excitability changes in specific chronic pain conditions, such as complex regional pain syndrome (Di Pietro et al., 2013, Nardone et al., 2018), central post-stroke pain (Betancur et al., 2021), or phantom-limb pain (Nardone et al., 2019), with variable findings.

The main TMS feature most consistently associated with chronic pain is SICI reduction in the motor cortex contralateral to the painful limb (Burns et al., 2016b, Eisenberg et al., 2005, Lefaucheur et al., 2006a, Schwenkreis et al., 2010, Sorel et al., 2018), suggesting that impairment of GABAergic neurotransmission could contribute to chronic pain pathophysiology. This notion is supported by findings of SICI normalization in response to therapeutic interventions that induce analgesic effects, such as motor cortex rTMS, peripheral nerve repetitive magnetic stimulation or ketamine infusion, with the degree of pain relief correlated with SICI improvement (Fierro et al., 2010, Lefaucheur et al., 2006a, Massé-Alarie et al., 2013, Mhalla et al., 2011, Sorel et al., 2018). It remains to be determined whether SICI reduction could serve as a biomarker to select candidates for analgesic neuromodulation, especially with regard to high frequency rTMS applied over the contralateral motor cortex, a therapeutic use of rTMS with high level of evidence of efficacy (Lefaucheur et al., 2020). The response to rTMS could be used as a surrogate biomarker to predict efficacy of invasive cortical stimulation (André-Obadia et al., 2014, Lefaucheur et al., 2011, Pommier et al., 2018).

Changes in motor cortex excitability may also be related to impaired descending inhibitory pain controls, as assessed by conditioned pain modulation (CPM) protocols. In fact, defective descending inhibitory controls (no pain reduction during CPM) have been associated with increased ICF (Botelho et al., 2016), reduced CSP duration (Tarragó et al., 2016) or greater SICI in fibromyalgia (Cardinal et al., 2019, Caumo et al., 2016). The

changes in cortical excitability correlated with increased serum brain-derived neurotrophic factor (BDNF) levels (Botelho et al., 2016, Cardinal et al., 2019, Caumo et al., 2016). It should be stressed that these changes in cortical excitability were opposite to that observed in chronic pain (reduced SICI and CSP duration), which cannot be explained through changes in descending controls.

Beyond cortical excitability measures, TMS can also be applied for mapping of motor cortical representation, notably using image-guided neuronavigation systems. Studies have been performed in stroke and phantom limb patients (Gunduz et al., 2020, Teixeira et al., 2021), although no clear association between motor map reorganization and presence or intensity of pain have been established beyond the plasticity of motor function in these conditions.

3.7. Multiple sclerosis

The probability that a patient with clinically definite MS (CDMS) has a prolonged CMCT is moderately high, with substantial variability across studies [56–93%] (Barker et al., 1986, Beer et al., 1995, Hess et al., 1986, Hess et al., 1987, Ingram et al., 1988, Jones et al., 1991, Kandler et al., 1991b, Mayr et al., 1991, Michels et al., 1993, Ravnborg et al., 1992, Rossini et al., 1989, van der Kamp et al., 1991). The large variability is explained by many factors, but most importantly by the selection and number of target muscles. Sensitivity increases if lower limb muscles are included (Jones et al., 1991, Jung et al., 2006, Kandler et al., 1991b, Mayr et al., 1991), and may also be influenced by the MS phenotype. Specifically, CMCT prolongation is more pronounced in progressive MS than in relapsing-remitting MS (RRMS) (Facchetti et al., 1997, Filippi et al., 1995, Humm et al., 2003, Kidd et al., 1998). Additionally, in RRMS or secondary progressive MS (SPMS) patients with lesions in the hand area of sensorimotor cortex, CMCT is prolonged (Madsen et al., 2022). Interestingly, CMCT can reveal a subclinical involvement of the corticospinal tracts in about 14% of multiple sclerosis patients (Di Lazzaro et al., 1999a).

Conventional measurements of MEP amplitude by single-pulse TMS add little to the sensitivity provided by CMCT measurements (Hess et al., 1987, Kandler et al., 1991b, Ravnborg et al., 1992). Triple-stimulation technique (TST, Fig. 2), however, have revealed frequent occurrence of central conduction failure due to focal central conduction block (Humm et al., 2004a) or loss of fastest-conducting corticospinal axons, even in the presence of normal CMCT and MEP measures (Hofstadt-van Oy et al., 2015, Magistris et al., 1999). TMS abnormalities, including prolonged MEP latency and CMCT as well as reduced MEP amplitude, was evident in MS patients without pyramidal tract signs (Kale et al., 2009), implying that the diagnostic utility of TMS is possibly underestimated in the currently recommended diagnostic criteria for MS (Thompson et al., 2018).

Axial muscles such as the diaphragm, paraspinal, pelvic floor and external sphincter muscles are often affected in MS. The corticospinal projection to these muscles is more difficult to assess, but TMS measures may reveal abnormalities (Brostrom et al., 2003, Eardley et al., 1991, Garland et al., 1996, Hashimoto et al., 2000, Lagueny et al., 1998, Miscio et al., 2003, Urban and Vogt, 1994).

Many studies indicated a significant correlation between CMCT or TST abnormalities and clinical motor signs or motor disability (Britton et al., 1991, Ingram et al., 1988, Jones et al., 1991, van der Kamp et al., 1991). CMCT measures integrated into a multimodal evoked potential (EP) score revealed close correlations with the Expanded Disability Status Scale [EDSS] (Bednarik and Kadanka, 1992, Fuhr et al., 2001). With longitudinal measurements, changes in EP score correlated with changes in EDSS (Ayache et al., 2015, Fuhr et al., 2001, Schlaeger R et al., 2012).

Multimodal EP scores, including baseline CMCT measurement, predicted the EDSS score in CDMS patients 2–3 years later (Fuhr et al., 2001, Schlaeger R et al., 2012) and long-term disability 14 years later (Schlaeger R. et al., 2012). Consequently, high multimodal EP scores at the time of measurement seem to be predictive of disability development.

TMS studies may also have a positive predictive value of conversion to MS, which may be an important management issue in patients with radiologically isolated or clinically isolated syndromes (CIS), who do not fulfill the current diagnostic criteria for MS (Thompson et al., 2018). To date, only one study has addressed this issue and demonstrated a longer CSP duration in CIS patients who developed CDMS within the next 24 months compared to those that did not develop CDMS (Pallix-Guyot et al., 2011). Other TMS measures (CMCT, MEP amplitude, RMT, iSP duration, transcallosal conduction time) did not differentiate between these two CIS groups (Pallix-Guyot et al., 2011).

Monitoring or predicting treatment efficacy is another potential utility of TMS. CMCT improves during an MS relapse treated with corticosteroids and correlates with clinical improvement (Fierro et al., 2002, Kandler et al., 1991a, La Mantia et al., 1994, Salle et al., 1992). Reduced MEP amplitude and MEP map size after a first-time motor relapse improves at 6-months follow-up, and this improvement is associated with improvement of hand dexterity (Chieffo et al., 2019). Reduced SAI improves in PPMS patients over one year of treatment with ocrelizumab, and this is associated with an improvement in the 9-hole peg test, a measure of sensorimotor hand function (Dubbioso et al., 2022a). Of relevance, the treatment response to 4-aminopyridine, an agent that improves gait function in SPMS (Goodwill et al., 2013), was predicted by prolonged CMCT to lower extremities (Zeller et al., 2014) and high RMT to a hand muscle (Ahdab et al., 2019).

TMS measures such as MEP onset latency variation (Britton et al., 1991, Fujihara and Miyoshi, 1998), TMS-frequency-dependent CMCT prolongation and MEP attenuation (Claus et al., 1992, Nielsen, 1997), greater increase in CMCT and more prolonged MEP amplitude reduction in response to fatiguing exercise (Coates et al., 2020, Liepert et al., 1996, Liepert et al., 2005, Petajan and White, 2000, Russo et al., 2015, Schubert et al., 1998, White and Petajan, 2004) have also been applied in MS, although their clinical utility remains to be determined. Additionally, reduction of SICF (Dubbioso et al., 2022a, Mori et al., 2013), SICI (Belvisi et al., 2022, Caramia et al., 2004, Conte et al., 2009, Vucic et al., 2012), SAI (Cucurachi et al., 2008, Dubbioso et al., 2022a), and prolonged CSP duration (Nantes et al., 2016), prolonged transcallosal conduction time (Boroojerdi et al., 1998a) and prolonged iSP duration (Boroojerdi et al., 1998b, Höppner et al., 1999, Jung et al., 2006, Schmierer et al., 2002, Schmierer et al., 2000) have also been reported in MS.

3.8. Stroke

Stroke is associated with abnormalities in TMS measures from both the ipsilesional and contralesional primary motor cortex. Most studies record MEPs from the upper limbs, and less is known about the effects of stroke on MEPs recorded from the lower limbs or swallowing muscles. The most obvious abnormality is an absence of MEPs in response to ipsilesional M1 stimulation. The absence of MEPs prevents measurement of motor threshold, MEP amplitude or latency, but still provides clinically important information.

Absent paretic upper limb MEPs at the early sub-acute stage of stroke strongly predicts worse motor recovery and outcomes, and at the chronic stage is related to worse motor performance (Boyd et al., 2017, Cicinelli et al., 1997, Karatzetzou et al., 2022, Stinear, 2017, Talelli et al., 2006, Traversa et al., 1997). The absence of MEPs

in the paretic lower limb at the early sub-acute stage is also linked to worse walking outcomes (Karatzetzou et al., 2022, Preston et al., 2021), although further research is needed. There is initial evidence that proximal upper limb muscles can recover strength despite an initial absence of MEPs, possibly via descending motor pathways that are less readily accessed by TMS such as the reticulospinal tract (Schambra et al., 2019). Further work is needed to understand the clinical implications of MEP absence in the proximal versus distal upper limb muscles.

The presence or absence of upper limb MEPs at the early sub-acute stage is a relatively simple biomarker that can inform individualized therapy plans (Rosso and Lamy, 2020, Stinear, 2017, Stinear et al., 2017a) and improve the efficiency and sensitivity of clinical trials (Stinear et al., 2018). The MEP status biomarker, however, has not yet been consistently defined. After a stroke, it is not uncommon to observe low amplitude MEPs that fail to meet traditional threshold amplitude criteria even at maximum stimulus intensity. Consequently, some studies define MEP + status as the presence of MEPs of any amplitude, on the basis that transmission of motor output from ipsilesional M1 is more clinically relevant than threshold stimulus intensity at the early sub-acute stage (Stinear et al., 2017a, Stinear et al., 2017b). It remains unclear whether initially absent or subthreshold MEPs that eventually meet the motor threshold criterion during subsequent recovery are associated with better outcome (Schambra et al., 2019, Talelli et al., 2006).

When MEPs are present in paretic muscles they can exhibit several abnormal features. Motor threshold is typically higher, MEP latency is delayed, MEP amplitude is smaller, and the slope of the stimulus–response curve is typically shallower (Bütefisch et al., 2008, Cicinelli et al., 1997, McDonnell and Stinear, 2017, Talelli et al., 2006, Traversa et al., 1997, Veldema et al., 2021). Motor map areas of the ipsilesional M1 are also typically smaller, and their center of gravity can be shifted anteriorly or posteriorly relative to maps of the contralesional M1 (Cicinelli et al., 1997, Lüdemann-Podubecká and Nowak, 2016). These abnormalities reflect the effects of stroke on the number of available cortical neurons and descending axons, and the excitability of surviving cortical neurons. More pronounced abnormalities in MEP threshold, latency, and amplitude, and motor map parameters are typically associated with worse motor performance at time of assessment (Boyd et al., 2017, Buetefisch et al., 2018, Duque et al., 2005, Lüdemann-Podubecká and Nowak, 2016, Talelli et al., 2006). Normalization of upper limb MEP parameters during the sub-acute stage of stroke is associated with improvements in upper limb motor performance (McDonnell and Stinear, 2017, Schambra et al., 2019, Stinear et al., 2015, Veldema et al., 2021). The clinical relevance of shifts in motor map center of gravity is not yet clear (Lüdemann-Podubecká and Nowak, 2016).

Measures of contralesional M1 excitability are typically within normal limits at the sub-acute stage of stroke (McDonnell and Stinear, 2017, Talelli et al., 2006). Contralesional excitability can become elevated at the chronic stage, perhaps reflecting prolonged asymmetric upper limb use after stroke (Xu et al., 2019). Studies at the chronic stage initially reported excessive pre-movement inhibition of the ipsilesional M1 by the contralesional M1 via the corpus callosum, and this was thought to contribute to poorer paretic upper limb performance (Duque et al., 2005, Murase et al., 2004). The resulting interhemispheric competition model posited that asymmetric interhemispheric inhibition between the M1s compounds reduced ipsilesional cortical excitability and hinders motor recovery. Subsequent studies (Bütefisch et al., 2008, Stinear et al., 2015, Xu et al., 2019) and meta-analyses (McDonnell and Stinear, 2017, Veldema et al., 2021) have shown that contralesional M1 excitability and interhemispheric inhibition of ipsilesional M1 are typically normal at the sub-acute stage of stroke. Abnormally elevated pre-movement interhemispheric inhibition of the ipsilesional M1 appears to develop as patients recover upper limb motor capacity and is therefore unlikely to be a useful therapeutic target (Xu et al., 2019). Furthermore, a recent review argues that transcallosal projections serve to shape the output of the opposite M1, rather than inhibit it (Carson, 2020).

Stimulation of the contralesional M1 can also produce MEPs and/or CSPs in paretic upper limb muscles. Ipsilateral MEPs can be more prevalent in the paretic upper limb, particularly the proximal muscles. In older adults without stroke, there is a positive association between upper limb strength and the ratio between ipsilateral and contralateral MEPs, with the former thought to be mediated by the reticulospinal tract (Maitland and Baker, 2021). There appears to be no clear relationship between ipsilateral responses to contralesional M1 stimulation and paretic upper limb performance (Hammerbeck et al., 2019). The neuronal populations responsible for ipsilateral MEPs and CSPs, and their clinical significance, remains under investigation.

Paired-pulse studies indicate that ipsilesional and contralesional SICI and LICI are typically abnormally low at the early sub-acute stage of stroke and normalize over subsequent weeks (Bütefisch et al., 2008, Dimyan and Cohen, 2010, Grigoras and Stagg, 2021, Huynh et al., 2016, McDonnell and Stinear, 2017, Talelli et al., 2006), though some longitudinal studies using threshold tracking techniques report persistently low SICI in both hemispheres (Huynh et al., 2013b, Huynh et al., 2016). Abnormally low SICI has also been reported in contralateral M1 following acute cerebellar stroke (Huynh et al., 2013a). Further research is required to establish the clinical significance of altered intracortical function after stroke, and whether it presents a viable therapeutic target (Agarwal et al., 2019).

3.9. Cerebellar disorders

In focal diseases affecting the cerebellar efferent system and comprising the cerebellar hemispheres, dentate and ventrolateral thalamic nuclei, CBI is decreased or absent (Kikuchi et al., 2012, Ugawa et al., 1997). In contrast, CBI was normal in patients with lesions of the afferent cerebellar inputs, including pontocerebellar, middle cerebellar peduncle and sensory-cerebellar pathways (Ugawa et al., 1994a, Ugawa et al., 1995a). TMS findings in chronic cerebellar neurodegenerative diseases are more complex, reflecting the underlying pathology. A reduction of CBI (at ISI 5 ms) was reported in spinocerebellar ataxia type 3 (SCA3), correlating with ataxia severity, and indicating the pathophysiological importance of cerebellothalamocortical tract dysfunction (Maas et al., 2021, Ugawa et al., 1997). CBI was normal in mildly affected SCA3 patients, suggesting that reduction of efferent pathway integrity is not a relevant feature of the earliest disease stages or that TMS only detects abnormalities after a certain threshold of dysfunction has been exceeded. A significant reduction of CBI (at ISI 5 and 6 ms) was also reported in the multiple system atrophy cerebellar subtype (MSA-C) and correlated with greater disease severity (Shirota et al., 2022). In early MSA-C with predominant dysfunction in the cerebellar afferent pathways, CBI is normal, implying a potential role for CBI as a biomarker of disease progression in neurodegenerative cerebellar diseases, although further research is required.

Reduction of CBI may herald the development of cerebellar dysfunction in other neurological disorders including progressive supranuclear palsy (PSP), essential tremor and focal dystonia. Specifically, an absence of CBI has been reported in PSP associated with degeneration of the dentate nuclei (Benussi et al., 2019b, Brusa et al., 2014, Shirota et al., 2010). While cerebellar ataxia is not a typical clinical feature of PSP, gait instability and falls could potentially be associated with dysfunction of cerebellar efferent

pathways (Benussi et al., 2019b). Reduction of CBI was also reported in essential tremor but did not correlate with tremor severity (Hanajima et al., 2016), suggesting that the cerebellar efferent pathways were either a primary pathogenic event or a compensatory physiological phenomenon in response to a pathogenic process outside the cerebellum. However, another study found normal CBI in essential tremor (Pinto et al., 2003).

Increased motor threshold was reported in acute cerebellar stroke, contralateral to the affected cerebellar hemisphere (Cruz-Martínez and Arpa, 1997), although others have reported normal thresholds (Huynh et al., 2013a, Liepert et al., 2004). Transient prolongation of CMCT has also been reported after cerebellar stroke (Cruz-Martínez and Arpa, 1997), with the argument that reduced size and increased dispersion of the efferent volleys accounted for the findings. A reduction of SICI has been reported in both the ipsi- and contralesional M1 (Huynh et al., 2013a), although others have documented an increase of SICI and reduction in ICF (Liepert et al., 2004). The discordant findings could be explained by variability in the cerebellar infarct territory, suggesting that distinct cerebellar regions and projections could potentially modulate cortical inhibitory and facilitatory circuits. Whether these modulatory effects represent adaptive changes or direct cerebellar damage, remains to be determined.

In degenerative cerebellar diseases, prolonged CMCT was reported in SCA1 in the upper limbs and SCA2 in the lower limbs, but not other SCA phenotypes (Tang et al., 2020), implying diverse pathological processes. Normal level of SICI has been reported in various forms of SCA (Ugawa et al., 1994b), while ICF was reduced (Berardelli et al., 2008, Liepert et al., 1998, Schwenkreis et al., 2002, Wessel et al., 1996). The ICF reduction was evident in SCA2 and SCA3, but not in Friedreich's ataxia, SCA1, and SCA6 patients. The reduction of ICF may be related to reduced excitatory drive form the deep cerebellar nuclei and reflecting underlying cortical pathology in SCA disorders. Reduction of SICI has also been reported in SCA 3 and SCA 14 patients (Farrar et al., 2016, Ganos et al., 2014), indicating a dysfunction of cortical inhibitory circuits, a notion supported by neuroimaging studies disclosing paracentral cortical thinning and atrophy (de Rezende et al., 2015, Etchebehere et al., 2001). The pathological and clinical heterogeneity of degenerative cerebellar disorders could account for the seemingly discordant TMS findings, although future studies should utilize multiple TMS parameters in a machine learning algorithm to develop prognostic and outcome biomarkers that can be readily translated into a clinical trial setting.

3.10. Facial nerve disorders

In unilateral idiopathic Bell's palsy, TMS studies have disclosed a reduced or absent MEP response when recording from the facial muscles (Glocker et al., 1994, Happe and Bunten, 2012, Lin et al., 2021, Schrader and Schrader, 1995, Schriefer et al., 1988). These TMS deficits developed in acute stages of Bell's palsy and persisted for months, even after the recovery of muscle weakness. Interestingly, the sensitivity of TMS was greater than electrical facial nerve stimulation, implying that the TMS stimulation site was proximal to the pathogenic lesion. While the prognostic utility of TMS abnormalities in Bell's palsy is limited (Lin et al., 2021), identifying a reduced or absent MEP responses may be of diagnostic potential, particularly in setting of relatively preserved peripheral motor amplitudes and prior to development of Wallerian degeneration. A normal TMS response with facial nerve stimulation combined with reduced MEP response with cortical stimulation may argue against a peripheral facial nerve lesion (Schriefer et al., 1988, Straub et al., 2000).

A reduction of facial MEP amplitudes is not specific to Bell's palsy and has been identified in other etiologies of facial nerve dysfunction, including infectious diseases, diabetes and neoplasms (Happe and Bunten, 2012, Nowak et al., 2005). Bilateral facial nerve dysfunction is associated with specific diseases, including Guillain–Barré syndrome, Lyme's disease, HIV infection, or sarcoidosis (Rösler et al., 1995). Prolonged transosseal conduction time, defined as latency differences between cortical MEP responses from electrically elicited facial nerve motor responses (stylomastoid stimulation), along with simultaneous slowing of conduction in the distal segments with MEP desynchronization, are characteristic features of demyelinating neuropathies, with or without accompanying facial weakness (Rösler et al., 1995, Schriefer et al., 1988). In facial nerve trauma, the MEP responses are typically absent, although if present imply nerve continuity and thereby a better prognosis (Har-El and McPhee, 2000). Paired pulse TMS was implemented as a prognostic tool in predicting the occurrence of hemifacial spam (HFS) after microvascular decompression (Park et al., 2018). In this protocol, a subthreshold CS delivered prior to a test stimulus resulted in MEP facilitation at ISIs 20, 25, and 30 s, and inhibition at ISIs 75 and 100 ms in healthy controls. Good surgical outcomes were reported after microvascular decompression when the physiological pattern of facilitation-inhibition was evident, suggesting prognostic utility, although further research is required.

3.11. Brain tumors

Brain tumors affect standard TMS parameters to varying degrees. Tumor growth in vicinity of the primary motor cortex may be associated with a complex pattern of changes (Sollmann et al., 2018). Consideration of tumor growth dynamics is important when interpreting TMS, as its likely that effects of time-dependent compensatory mechanisms may be assessed. Due to highly variable tumor growth dynamics and individual predispositions to neuroplasticity, clinically heterogeneous findings may be evident. Increased RMT of both the tumorous and healthy hemispheres was associated with a worse motor outcome (Rosenstock et al., 2022). In patients with small tumor-to-corticospinal tract distances, a disturbance in motor excitability (interhemispheric RMT ratio < 90% or > 110%) is associated with a higher risk of new motor deficits either from surgery or tumor growth (Rosenstock et al., 2017). A greater distance between the lesion and motor hotspot as well as the presence of MEP responses 1 week after surgery have been associated with improved motor recovery, suggesting their utility in prognostication (Takakura et al., 2017).

Of relevance, microstructural impairment of white matter correlates with a deterioration of the motor excitability profile, resulting in significantly higher RMTs in the ipsilateral motor cortex (Mirchandani et al., 2020). Fine granular analysis of MEPs has been shown to be more sensitive to tumor-related changes than classical analysis, with spectral analysis of EMG responses showing early impairment of cortical excitability in brain tumors (Machetanz et al., 2021). Specifically, brain tumors affect corticospinal transmission resulting in temporal and spectral MEP desynchronization which correlates with poor dexterity performance.

Recent advances in TMS technology have enabled M1 mapping with a two-coil transducer without moving the coil. This approach has resulted in electronically controlled modelling of the applied electric field over a wider cortical area allowing for improved spatial and temporal control of the stimulation (Koponen et al., 2018). Multicoil TMS systems are being developed that can tune electronic stimulation to a cortical region without moving the coil enabling time-coupled application of stimuli with unlimited E-field orientations and strengths (Nieminen et al., 2022). This would enable excitability measurements of tumorous motor cortical areas with unprecedented control and significantly improve already

promising neuromodulatory interventions in brain tumor patients (Ille et al., 2021a).

Closed-loop configurations with automated modification of stimulation depending on neurophysiological and/or behavioral measures have received increasing attention in recent years. EMG-driven TMS allows online adaption of stimulation settings to allow optimized analysis of specific excitability measures (Meincke et al., 2016). EEG feedback for brain state-dependent synchronization of the TMS stimulus allows for better control of the TMS-brain interaction and therefore more reliable assessments of tumor effects on brain excitability (Zrenner et al., 2022). Given the clinical utility of RMT, novel TMS technologies have the potential to interrogate the effects of brain tumor on motor function even more accurately and at an individualized level. In the future, this could provide TMS with an even more important role for tailored treatment pathways including neuromodulatory interventions during the treatment of motor eloquent brain tumors.

Using TMS to outline language-related areas has been made possible with advances in neuronavigation (Lioumis et al., 2012). Comparison of neuronavigated TMS to intraoperative mapping showed a high negative predictive value (Krieg et al., 2014, Picht et al., 2013). Nonetheless, the combination of cortical mapping and subcortical tractography, seeded from those areas, lead to a broader clinical application for approach guidance but also risk assessment. Various studies disclosed high reliability for preoperative risk prediction, particularly for the ratio between left and right-sided language production, connectivity between hemispheres, as well as proximity between tumor and subcortical tracts (Ille et al., 2016, Sollmann et al., 2019, Sollmann et al., 2017). In adults, comparison data also provides some hint that language eloquent perisylvian tumors can be resected with the same functional and oncological results based on neuronavigated TMS data instead of performing awake surgery (Ille et al., 2021b), although further studies are required. Clinical mapping using neuronavigated TMS may be of utility in pediatric patients as well down to the age of 6 years (Rosenstock et al., 2020). Such pediatric applications further promote the spread of neuronavigated TMS in neuro-oncology.

3.12. Disorders of consciousness

As anticipated in section 2.5, directly probing the internal state of cortico-thalamic circuits with TEP provides relevant information in disorders of consciousness. TEPs reflect the reactivity of the neuronal population under the TMS coil as well as remote and re-entrant responses from connected populations with different electrophysiological properties (Massimini et al., 2005, Rosanova et al., 2009). In this way, TMS-EEG may be used to assess by a causal perspective to what extent distributed and differentiated groups of neurons interact to produce complex dynamics. Based on theoretical neuroscience (Tononi and Edelman, 1998) and empirical evidence (Sarasso et al., 2021), this kind of complexity, arising from the coexistence of functional integration and functional differentiation, is considered a fundamental prerequisite for consciousness. Consequently, specific TMS-EEG-based measures, such as Perturbational Complexity Index (PCI), have been developed to assess recovery of consciousness in patients emerging from coma. In this section, we will present the rationale and basic methods for computing PCI and describe its application in patients with disorders of consciousness, highlighting its advantages and some methodological cautionary notes.

3.12.1. Computing PCI

Upon falling asleep and with general anesthesia, the complex waveforms and spatio-temporal dynamics characterizing TEPs during wakefulness are replaced by a simpler response, characterised by a positive–negative deflection centered around the stimulated area (Ferrarelli et al., 2012, Massimini et al., 2005, Sarasso et al., 2015). Notably, a similar change in TEPs characteristics can be observed also in pathological loss of consciousness, whereas the return of complex waveforms is associated with recovery (Ragazzoni et al., 2013, Rosanova et al., 2012). PCI has been devised to capture these changes (Casali et al., 2013).

Starting from TEPs, computing PCI involves a few steps (i) performing cortical source modelling of average scalp responses (ii) applying statistics to extract a binary matrix that describes the spatial–temporal pattern of deterministic cortical activation and (iii) compressing this binary matrix using the Lempel and Ziv algorithm (Lempel and Ziv, 1976) to quantify its complexity. Local (low integration) or stereotypical (low differentiation) responses can be effectively compressed, resulting in low PCI values. On the contrary, responses that are both integrated and differentiated are less compressible, resulting in high PCI values.

3.12.2. PCI validation and application

Before applying it to disorders of consciousness patients, PCI was first calibrated in healthy subjects and patients who could report about their state of consciousness, including wakeful and dreaming experiences as well as deep sleep and general anesthesia. Such calibration in a large benchmark population (n = 150) enabled a definition of an operational cut-off (PCI*=0.31) above which consciousness is invariably present. This empirical PCI cut-off was then applied to infer the presence of consciousness in challenging disorders of consciousness patients showing minimal, or no behavioural signs of consciousness (Bodart et al., 2017, Casarotto et al., 2016, Sinitsyn et al., 2020). PCI showed an unprecedented sensitivity (about 95%) in identifying Minimally Conscious State patients which show minimal behavioural outputs. In these patients, high PCI values reliably detected the presence of consciousness even when severely abnormal EEG patterns, characterized by slow waves, are present (Fig. 5A, B). Crucially, PCI also allows an informative stratification of patients that are completely unresponsive, such as patients in a Vegetative State, otherwise called Unresponsiveness Wakefulness Syndrome. Within the population identified by this behavioral label, TEPs reveal the existence of three different electrophysiological states (Fig. 5C): (i) a state with no significant EEG response to TMS (no response patients), (ii) a low-complexity state similar to that observed in non-rapid eye movement (NREM) sleep and anesthesia unconsciousness (low-complexity patients) and (iii) a high-complexity state similar to that observed in conscious awake or dreaming subjects (high-complexity patients) (Casarotto et al., 2016).

This TMS-EEG-based stratification has interesting pathophysiological implications and is clinically informative. The "no" response subgroup is typically composed of TMS of patients who suffered from post-anoxic damage and diffuse cortical necrosis, once called 'apallic syndrome'. The low-complexity group encompasses patients of variable aetiology in whom portions of the cerebral cortex retain some degree of structural integrity, activity and reactivity. Interestingly, although these patients are awake, as judged by eye opening, residual circuits appear to be blocked in a pathological sleep-like state whereby cortical reactivity is limited to a low-complexity positive–negative deflection. Notably, in these patients, time–frequency analysis of TEPs point to specific neuronal dynamics underlying loss of complexity-the inescapable occurrence of a silent period (OFF-period) after the initial activation triggered by TMS. This tendency of cortical neurons to plunge into an OFF-period upon receiving an input, also known as cortical bistability, is a mode typical of NREM sleep, that may pathologically intrude in the awake brain after injury, leading to a massive disruption of network complexity in many unresponsive patients. As shown by longitudinal measurements, the reduction of cortical bistability

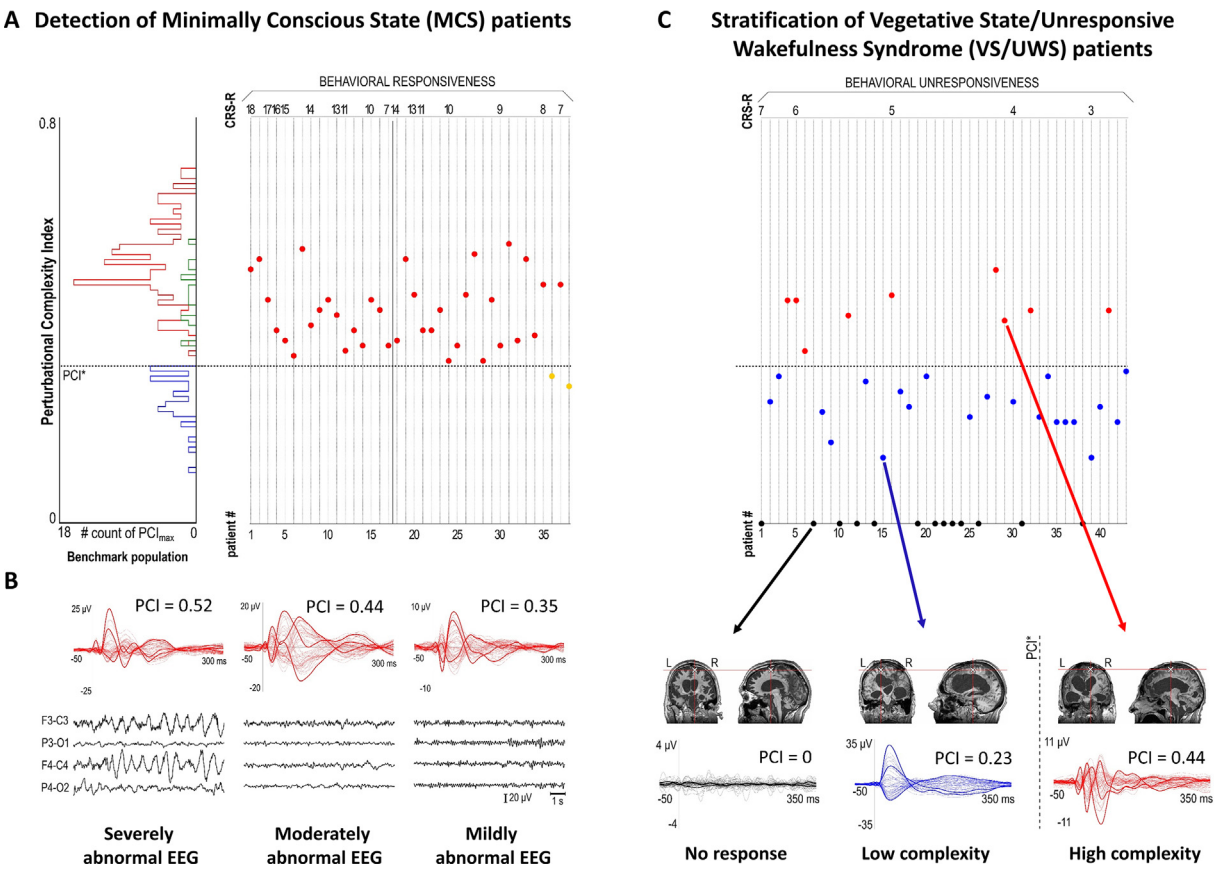

Fig. 5. TMS-EEG and Perturbational Complexity Index (PCI) in a benchmark population, in minimally conscious state and Unresponsiveness Wakefulness Syndrome patients. (A) Distribution of maximum PCI values computed in the benchmark population (left) in the absence of subjective report (blue line) and in the presence of subjective report (delayed, green line; immediate, red line). The dashed horizontal line indicates the cut-off (PCI*) optimally discriminating consciousness from unconsciousness in the benchmark population. The scatter plot shows the maximum PCI values obtained in individual minimally conscious state (n = 38) patients, sorted by the Coma Recovery Scale-Revised (CRS-R). For each patient, the PCI is represented by a color-filled circle (Modified from Casarotto et al., 2016). (B) The upper row shows TMS evoked potentials [TEPs] (butterfly plot of all EEG channels superimposed, with three illustrative channels highlighted by bold red traces) together with the corresponding PCI values in three representative minimally conscious state patients with PCI higher than PCI*. The lower row shows 10 s of spontaneous EEG recorded from four bipolar EEG channels (F3-C3, P3-O1, F4-C4, and P4-O2) in the same patients. Note that despite having all PCI values above PCI*, minimally conscious state patients displayed patterns of spontaneous background EEG activity that were severely abnormal (left), moderately abnormal (center), and mildly abnormal (right) (Modified from Casarotto et al., 2016). (C) PCI-based stratification of Unresponsiveness Wakefulness Syndrome patients. The scatter plot shows all the maximum PCI values obtained in individual Unresponsiveness Wakefulness Syndrome (n = 43) patients. For each patient, the PCI is represented by a colour-filled circle. Unresponsiveness Wakefulness Syndrome patients could be stratified into three subgroups according to PCI values: high-complexity patients with PCI > PCI* (n = 9, red), low-complexity patients with PCI < PCI* (n = 21, blue), and no-response patients with PCI = 0 (n = 13, black). The lower row shows the structural MRI, the TEP and the corresponding PCI value reported for a representative subject of each subgroup (modified from Casarotto et al., 2016).

parallels, and sometimes anticipates, recovery of network complexity and behavioural responsiveness (Rosanova et al., 2018, Rosanova et al., 2012). Notably, a similar intrusion of sleep-like reactivity can also be observed locally in the perilesional area of stroke patients, possibly leading to selective loss of motor/cognitive function (Sarasso et al., 2020, Tscherpel et al., 2020). Finally, the finding of a third subgroup of unresponsive patients showing high-complexity, entails important clinical and ethical implications. Indeed, this condition indicates a capacity for consciousness, not expressed in behaviour due to pathological impairment of sensory and/or motor functions, and indicates a better chance of recovery (Casarotto et al., 2016, Rosanova et al., 2018, Rosanova et al., 2012).

3.12.3. Advantages of TMS-EEG in disorders of consciousness patients and cautionary notes

The high-sensitivity of TMS-EEG above and beyond behavioural responsiveness and spontaneous EEG patterns may be ascribed to different factors. First, this technique allows by-passing sensory processing, as well as motor functions, which are often impaired after severe brain injury. Second, it does not require any active engagement in specific tasks, a demand often unmet by patients with severe cognitive impairment. Third, the high signal-to-noise ratio of TEPs allows detecting residual network complexity even when this is masked by high-amplitude delta waves in the spontaneous EEG (Frohlich et al., 2021).

The flip side is that applying TMS-EEG to disorders of consciousness demands stringent requirements and special methodological caution. A first key requirement is that TEPs must adhere to the quality criteria illustrated in section 2.5. This not only entails a high-amplitude (around 10 microvolts) initial response but also requires collecting a number of trials that is sufficient to obliterate the increased baseline variability imposed by spontaneous slow waves, which are often present after brain injury. Since collecting hundreds of trials currently takes from 5 to 10 minutes, TMS-EEG measures of complexity cannot be used to monitor short term fluctuations in the state of consciousness, such as fleeting dreams reports during sleep (Nieminen et al., 2016) and anaesthesia. Finally, given that the current calibration of PCI in subjects providing negative delayed report during sleep and anaesthesia cannot

rule out the presence of fleeting dreams, low PCI values cannot be used to rule out consciousness but only to reveal the presence of it in unresponsive patients.

3.13. Functional neurological disorders

Functional neurological disorders are common and may present with almost any neurological symptom. One important feature for making the diagnosis is incongruence or incompatibility with features of other neurological disorders (Hallett et al., 2022). TMS may supplement clinical assessment in functional neurological disorders. While there are some promising small studies, none of the methods have moved into clinical practice.

In patients with functional weakness, discordant TMS findings have been reported, with some studies documenting normal RMT, SICI, and ICF (Liepert et al., 2008, 2009), while others established an increase in RMT and SICI (Benussi et al., 2020e). Differences are small and could be different from stroke patients with comparable reduction in muscle strength. Separately, an increase in MEP duration with voluntary contraction (30% maximal force) has been reported in stroke and healthy controls, decreased in MS, while no change was evident in functional neurological disorders paretic patients (Brum et al., 2015), suggesting potential utility.

Changes in MEP amplitude and RMT with movement imagery of target muscle may also be of diagnostic utility in functional neurological disorders. In healthy controls, imagining movement of congruent muscle in the contralateral limb increases the MEP amplitude and reduces RMT (Facchini et al., 2002), while negative motor imagery resulted in MEP amplitude reduction (Sohn et al., 2003). Motor imagery was associated with more pronounced motor output enhancement in the hemisphere in stroke (Cicinelli et al., 2006), contrasting with paretic functional neurological disorders patients (weak upper limb) whereby the MEP amplitude is reduced (Liepert et al., 2008, 2009, 2011).

In dystonic functional neurological disorder patients, abnormalities of TMS measures have been well documented, including a reduction of SICI, LICI, and CSP duration (Espay et al., 2006). Additionally, the cutaneous silent period was increased, and forearm reciprocal inhibition reduced. In contrast, SAI and LAI were comparable to healthy controls for functional dystonia, while a similar degree of SICI reduction was evident in both functional and organic dystonia (Quartarone et al., 2009). As such, the utility of TMS in dystonic functional neurological disorders seems limited.

4. Conclusion

The various TMS techniques have demonstrated strong clinical and diagnostic utility in a variety of neurological diseases, including neurodegenerative, movement, autoimmune and episodic disorders as well as spinal cord and functional neurological diseases. Novel TMS techniques, such as threshold tracking TMS, has demonstrated diagnostic utility in ALS and has been recently commercialized. TMS-EEG is an emerging technique with the ability to directly assess cortical function, bypassing subcortical and peripheral neurological systems. In addition to established utility as a diagnostic biomarker in neurodegenerative disease, TMS measures appear suitable for incorporation as therapeutic (i.e., monitoring and outcome) biomarkers of clinical efficacy in future clinical trials. Multicenter studies incorporating larger patient cohort sizes and more homogenous study populations in terms of disease characteristics and treatment will help further clarify utility of the novel TMS techniques.

Conflict of interest

A Benussi was partially supported by the Airalzh-AGYR2020, by Fondazione Cariplo (grant n° 2021-1516), and by the Fondation pour la Recherche sur Alzheimer. **M. Hallett** is an inventor of a patent held by NIH for the H-coil for magnetic stimulation for which he receives license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Board of Brainsway (unpaid position). **S. Kreig** reports being a consultant for Brainlab and receiving honorarium for lectures provided for Nexstim and Inomed. **M Massimini** is a co-founder and shareholder of Intrinsic Powers, a spin-off of the University of Milan, Milan, Italy. **T. Picht** served as a consultant for the TMS system manufacturer Nexstim Oy, Helsinki, Finland. **U. Ziemann** reports receiving a grant from Takeda Pharmaceutical Company Ltd., and consulting fees CorTec GmbH. The other authors have no potential conflicts of interest to disclose.

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