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Review

Emergent technologies and applications of TMS and TMS-EEG in clinical neurophysiology for early and differential diagnosis: IFCN handbook chapter☆

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ABSTRACT

This chapter examines how emerging neurophysiological technologies are transforming the early and differential diagnosis of neurological disorders. While imaging and fluid biomarkers have greatly advanced the field, they remain limited by cost, invasiveness, and their inability to directly capture dynamic brain activity. Neurophysiological techniques, particularly transcranial magnetic stimulation (TMS) and TMS combined with EEG, offer a unique, non-invasive means of probing cortical excitability, connectivity, and plasticity with millisecond precision.

Recent technological and analytical breakthroughs are moving these approaches from research laboratories into clinical practice. By detecting subtle network dysfunctions that precede structural degeneration, they open the possibility of identifying disease in its prodromal or even presymptomatic stages, when interventions may be most effective. This chapter outlines the principles of advanced TMS paradigms and TMS-EEG and explores their application across a range of conditions, including amyotrophic lateral sclerosis, dementias, and movement disorders. It also highlights how integrating neurophysiological measures with blood-based biomarkers and computational tools, such as machine learning, can enhance diagnostic accuracy and guide individualized treatment strategies.

Together, these innovations establish neurophysiology as a cornerstone of precision neurology, linking mechanistic insights to clinical decision-making and enabling earlier diagnosis, improved patient stratification, and more targeted therapeutic interventions.

1. Introduction

Neurological disorders constitute a major global health burden, affecting more than three billion individuals worldwide and representing the leading cause of disability-adjusted life years (Steinmetz et al., 2024). This burden continues to grow with population ageing and improved survival from other chronic diseases, underscoring the urgent need for more effective diagnostic and therapeutic strategies (Steinmetz et al., 2024).

A central challenge in neurology is that many disorders are typically diagnosed at advanced stages, when extensive neuronal loss has already occurred and therapeutic windows have narrowed or closed (Hampel et al., 2023). Recent advances in disease-modifying treatments across several conditions highlight that interventions are most effective when initiated early, ideally before the onset of overt symptoms (Benatar et al., 2022; van Dyck et al., 2023; Sims et al., 2023). Consequently, the field is witnessing a paradigm shift from traditional, symptom-based diagnosis toward biomarker-guided approaches that can identify disease processes in their presymptomatic or prodromal phases (Hampel et al., 2023).

Conventional diagnostic tools, such as clinical examination, neuroimaging, and fluid biomarkers, have undoubtedly advanced the field but remain limited in sensitivity, specificity, accessibility, and cost-effectiveness (Schöll et al., 2024). Structural and molecular imaging

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may miss early disease-related changes; cerebrospinal fluid assays, while biochemically informative, are invasive and not universally accessible; and blood-based biomarkers, though highly promising, are still subject to technical and biological confounders and are not yet widely available in routine practice (Engelborghs et al., 2017; Fontana et al., 2023; Han et al., 2020; Schöll et al., 2024). Clinical assessment, while indispensable, often identifies pathology only once functional impairment is clinically apparent (Small, 2025).

Clinical neurophysiology provides a complementary and uniquely powerful approach to address these limitations (McMackin et al., 2019). Techniques such as electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and TMS-EEG directly capture the functional state of the nervous system with millisecond temporal resolution (Beniczky and Schomer, 2020; Gross, 2019; Hernandez-Pavon et al., 2023; Rossini et al., 2015). These modalities can detect subtle network dysfunctions that precede overt structural changes, are relatively low-cost, and are suitable for repeated assessments over time (McMackin et al., 2019). Importantly, they are widely available and can be applied in both specialized and general clinical settings, offering practical advantages for longitudinal monitoring and large-scale implementation.

Among these methods, the present chapter focuses on TMS and its integration with EEG (TMS-EEG), rather than on resting-state EEG or MEG. This focus is deliberate: while resting-state recordings provide valuable correlational measures of spontaneous neural activity, TMS-based paradigms uniquely allow the direct perturbation and measurement of cortical circuits, thereby establishing causal links between neural excitability, connectivity, and behaviour. Moreover, recent technological advances, including threshold-tracking protocols, paired-pulse measures, and perturbation-based EEG connectivity analyses, have enabled TMS and TMS-EEG to generate reproducible, disease-specific biomarkers that are now entering clinical translation. These features position TMS-derived techniques as the most promising neurophysiological tools for bridging mechanistic insight and diagnostic utility across neurodegenerative and movement disorders.

This chapter therefore examines recent technological and methodological advances in TMS and TMS-EEG and their applications in the early and differential diagnosis of neurological diseases. We will discuss how these approaches can quantify cortical excitability, inhibition, facilitation, and plasticity, and how they complement existing imaging and molecular biomarkers. By situating these developments within the broader diagnostic landscape, we aim to highlight the emerging role of neurophysiological biomarkers as key components of precision neurology.

2. Emergent neurophysiology techniques for early and differential diagnosis

Recent advances in neurophysiology have provided powerful tools for directly assessing cortical excitability, network connectivity, and circuit-level dysfunction (Rossini et al., 2015; Vucic et al., 2023). These approaches yield objective biomarkers capable of capturing pathophysiological changes at prodromal or even presymptomatic stages, often before clinical manifestations are evident. Among them, TMS has emerged as one of the most versatile and informative methods (Hallett, 2007). By inducing transient electrical currents in targeted brain regions, TMS offers a non-invasive means of probing human cortical physiology. Before addressing specific applications, it is useful to briefly summarize the principal measures and stimulation protocols, which will be referenced in subsequent sections of this chapter. By varying the mode and timing of stimulation, TMS can selectively interrogate distinct neurotransmitter systems, inhibitory and excitatory circuits, and plasticity mechanisms, providing a comprehensive characterization of cortical function (Ziemann, 2013).

Due to its biophysical properties, TMS activates cortical pyramidal cells primarily in a *trans*-synaptic manner (Di Lazzaro et al., 1998). This characteristic, in contrast with transcranial electrical stimulation (Merton and Morton, 1980), makes TMS particularly suited for the study of intracortical excitability. Depending on the protocol, it can be applied to investigate both local and distributed circuits. Single-pulse paradigms offer global measures of corticospinal excitability and the intrinsic excitability of pyramidal neurons, whereas paired-pulse protocols, where a conditioning stimulus precedes a suprathreshold test stimulus at variable interstimulus intervals (ISIs), enable the study of specific inhibitory or facilitatory interactions within cortical networks (Rossini et al., 2015). When stimulation is repeated over time, as in rTMS protocols, it can induce sustained modulation of cortical excitability through mechanisms that resemble synaptic plasticity (Pascual-Leone et al., 1994). Although most studies have targeted the primary motor cortex (M1) and measured motor-evoked potentials (MEPs) as an output (Dubbioso et al., 2021), similar paradigms can be extended to non-motor regions by combining TMS with EEG and recording TMS-evoked potentials (TEPs) (Thut and Pascual-Leone, 2010; Tremblay et al., 2019). Fig. 1 provides an overview of the principal TMS paradigms discussed in this section, including canonical paired-pulse measures as SICI, ICF, LICI, and SAI, and representative TMS-evoked potentials (TEPs) recorded with TMS-EEG. Together, these approaches enable the quantification of inhibitory and excitatory dynamics as well as large-scale cortical reactivity.

2.1. Core TMS single-pulse and paired-pulse measures

Within single-pulse protocols, the motor threshold (MT) represents the minimum intensity at which MEPs can be reliably elicited and is considered a global index of corticospinal excitability (Rossini et al., 2015). A discrepancy between reduced excitability to TMS and preserved excitability to transcranial electrical stimulation, which directly activates corticospinal axons, is interpreted as selective impairment of intracortical excitatory connections (Di Lazzaro et al., 1998). Another classical measure is the cortical silent period (CSP), observed as a pause in voluntary EMG activity following a suprathreshold TMS pulse. While its early component may reflect spinal refractoriness, the later portion is attributable to cortical inhibition mediated by $GABA_B$ receptors (Cantello et al., 1992; Chen et al., 1999; Werhahn et al., 1999).

Short interval intracortical inhibition (SICI) is a sensitive TMS biomarker of motor cortex excitability within M1 and is the most frequently used paired-pulse TMS paradigm (Kujirai et al., 1993), with the reliability and reproducibility of mean SICI in healthy populations recently confirmed (Matamala et al., 2018), suggesting clinical utility. SICI is elicited when a preceding subthreshold conditioning stimulus (CS) suppresses the MEP produced by a subsequent suprathreshold test stimulus (TS) at ISIs of 1–7 ms. Using the conventional "constant stimulus" method, this results in a reduced MEP amplitude compared with that produced by an unconditioned TS (Kujirai et al., 1993). A threshold tracking paired-pulse TMS technique was later developed, in which the TS is adjusted to maintain a fixed MEP amplitude (0.2 mV $\pm$ 20 %) while ISIs are varied in either a sequential ascending order (Vucic and Kiernan, 2006) or a pseudorandom parallel fashion (Tankisi et al., 2021a). For the threshold tracking TMS paradigm, SICI is reflected by the requirement of a higher conditioned test stimulus intensity to generate and maintain the target MEP response (when compared to unconditioned TS) between 1-to-7 ms. Two phases of SICI have been described: a smaller phase at an ISI of $\sim$ 1 ms and a larger phase at ISIs of 2.5–3 ms, although the exact physiological mechanisms underlying these phases remain a matter of debate (Fisher et al., 2002; Vucic and Kiernan, 2006). Notwithstanding ongoing debate, multiple lines of evidence support a cortical origin of SICI, most likely mediated by inhibitory interneuronal circuits acting through $GABA_A$ receptors. Additional mechanisms have also been proposed, including increased axonal refractoriness and shunting inhibition arising from the opening of channels in proximal dendrites targeted by incoming afferents (Chen, 2004; Fisher et al., 2002; Hanajima et al., 2003; Di Lazzaro and Rothwell, 2014; Paulus and Rothwell, 2016; Vucic

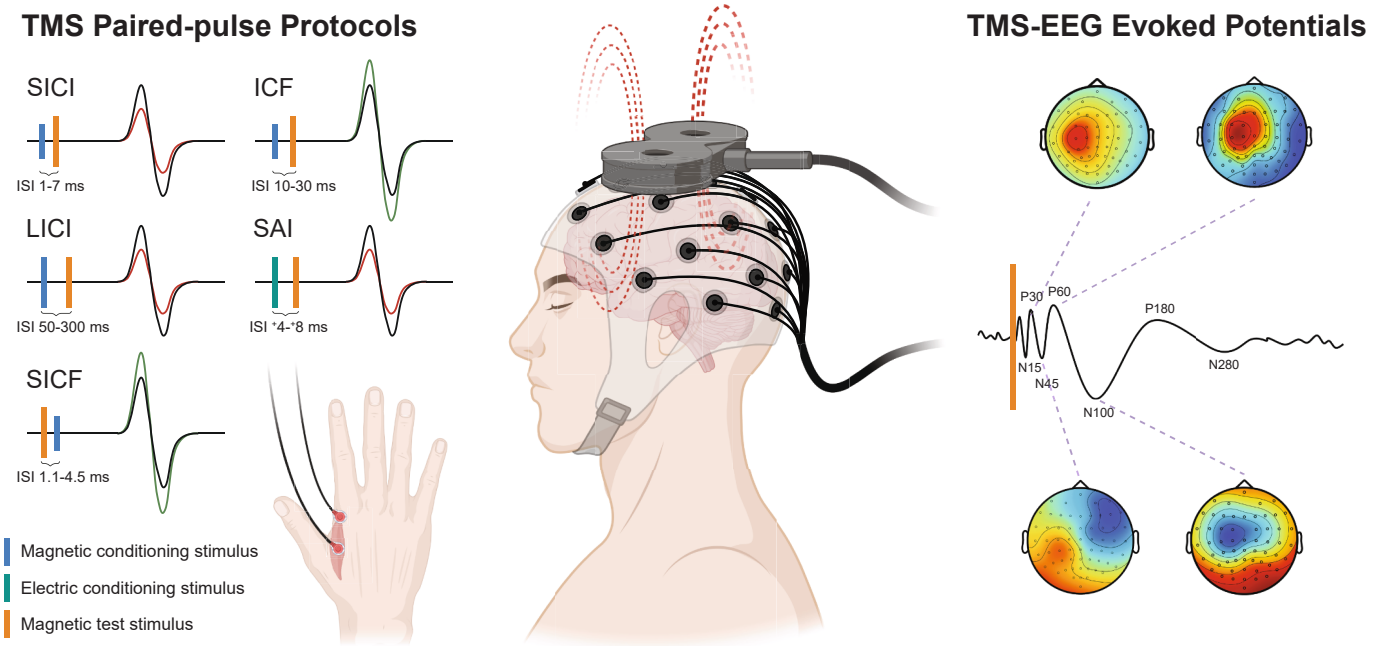

Fig. 1. TMS paired-pulse paradigms and TMS-EEG evoked potentials Schematic representation of the principal transcranial magnetic stimulation (TMS) paradigms used to assess cortical excitability and inhibition. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are elicited using paired magnetic stimuli with interstimulus intervals (ISIs) of 1–7 ms and 10–30 ms, respectively; long-interval intracortical inhibition (LICI) employs ISIs of 50–300 ms; short-latency afferent inhibition (SAI) combines a peripheral electrical conditioning stimulus applied to the median (or ulnar) nerve at the wrist with a magnetic test pulse delivered at ISIs of + 4 to + 8 ms relative to the latency of the N20 component of the somatosensory evoked potential (SEP); short-interval intracortical facilitation (SICF) is obtained when a suprathreshold pulse (S1) is followed by a subthreshold pulse (S2) at ISIs of approximately 1.1–1.5, 2.3–3.0, and 4.1–4.5 ms, producing distinct facilitation peaks. The relative height of the bars represents stimulus intensity with respect to the resting motor threshold (short = subthreshold; long = suprathreshold). Representative TMS-evoked potentials (TEPs) recorded with TMS-EEG following stimulation of the left primary motor cortex are shown, including early (P30, N45), middle (P60, N100, P180), and late (N280) components reflecting distinct excitatory and inhibitory processes. Abbreviations: ICF = intracortical facilitation; ISI = interstimulus interval; LICI = long-interval intracortical inhibition; N = negative deflection; P = positive deflection; SAI = short-latency afferent inhibition; SICI = short-interval intracortical inhibition; TEP = TMS-evoked potential; TMS = transcranial magnetic stimulation; TMS-EEG = combined transcranial magnetic stimulation and electroencephalography.

et al., 2011; Vucic et al., 2009; Ziemann et al., 2015). More recently, it was reported that physiologically distinct interneuronal circuits of variable cortical orientation and thresholds also contribute to SICI (Pavey et al., 2023).

Long-interval intracortical inhibition (LICI), typically elicited at ISIs of ~ 50–200 ms, is mediated by $GABA_B$ mechanisms and may share common pathways with the CSP (Claus et al., 1992; Di Lazzaro et al., 2002a; Nakamura et al., 1997; Valls-Solé et al., 1992). SICI and LICI are functionally distinct, as supported by pharmacological dissociation and the lack of correlation between them (McDonnell et al., 2006; Sanger et al., 2001; Ziemann, 2004; Ziemann et al., 2015).

Short-interval intracortical facilitation (SICF) reflects the activity of higher-threshold cortical circuits, typically elicited when the CS is set at or above threshold (Chen et al., 2008; Ziemann et al., 1998). Utilising the constant stimulus method, three distinct SICF peaks have been identified at discrete ISIs: 1.1–1.5, 2.3–3.0, and 4.1–4.5 ms corresponding to SICF-1, SICF-2, and SICF-3. More recently, a threshold tracking TMS paradigm was developed in which both the CS and TS were set to threshold, and SICF was quantified by the reduction in TS intensity required to maintain a target MEP amplitude of 0.2 mV [±20 %] (Van den Bos et al., 2018). As with the constant stimulus method, SICF was observed at ISIs of 1–5 ms, with two facilitation peaks typically occurring at approximately 1.5 ms and 2.5–3 ms. The precise physiological mechanisms mediating SICF remain to be fully elucidated; converging evidence indicates that SICF arises from facilitatory interactions among I-waves at the motor cortex (Hanajima et al., 2002; Ziemann et al., 2015, 1998), while disinhibition of inhibitory neuronal circuits has also been proposed (Wagle-Shukla et al., 2009). The former notion is supported by TMS modelling studies (Rusu et al., 2014) and the observed periodicity of the specific peaks which occur at 1.5 ms (~660 Hz), being consistent with the I-wave frequency (Amassian et al., 1987). Pharmacological TMS studies have implicated multiple neurotransmitter systems in SICF, reinforcing its cortical origin (Ilić et al., 2003, 2002; Korchounov and Ziemann, 2011; Di Lazzaro and Ziemann, 2013; Ziemann et al., 2015). The facilitating effects of SICI highlights the role of cortical circuitry (Wagle-Shukla et al., 2009), likely through disynaptic inhibition. Notably, the stimulation intensities and interstimulus intervals that elicit SICF overlap with those of SICI, and activation of SICF may account for the attenuation of SICI observed at higher CS intensities (Ni et al., 2013; Peurala et al., 2008).

Central cholinergic circuits can be probed with short-latency afferent inhibition (SAI), a protocol in which a peripheral afferent stimulus suppresses MEPs evoked by M1 stimulation at latencies of 2–8 ms (Dubbioso et al., 2019, 2017; Tokimura et al., 2000). The sensitivity of SAI to muscarinic antagonists and acetylcholinesterase inhibitors demonstrates its dependence on central cholinergic transmission (Di Lazzaro et al., 2005, 2000), while studies also point to complex interactions with GABAergic and dopaminergic systems (Berlanga et al., 2005; Di Lazzaro et al., 2007a; De Marco and Venneri, 2018; Martorana et al., 2013, 2009; Nobili et al., 2017).

In addition to local circuits, TMS can be used to probe connectivity between cortical regions. Interhemispheric inhibition (IHI), also known as transcallosal inhibition, measures the suppressive effect of conditioning stimulation in one M1 on contralateral responses at ISIs of 6–50 ms (Ferbert et al., 1992; Di Lazzaro et al., 1999). Early and late components (s-IHI and l-IHI) appear to involve different mechanisms, with

pharmacological evidence suggesting a role for $GABA_B$ receptors in the late component (Daskalakis et al., 2002; Irlbacher et al., 2007). Related measures such as the ipsilateral silent period (iSP) provide complementary insight into transcallosal inhibition during voluntary contraction (Giovannelli et al., 2009; Lee et al., 2007). Connectivity has also been studied between premotor and motor cortices (Buch et al., 2010), posterior parietal and motor regions (Koch et al., 2007), and cerebellum and M1 (Oliveri et al., 2005), demonstrating the versatility of dual-site TMS. EEG methods can extend these observations by quantifying oscillatory synchrony across regions (Rossini et al., 2020). The integration of TMS with EEG further expands the range of measures by capturing TEPs across cortical areas and characterizing oscillatory responses in multiple frequency bands, such as alpha, beta, and gamma (Assenza et al., 2017; Canali et al., 2017; Pigorini et al., 2011; Rosanova et al., 2009; Tremblay et al., 2019). This approach not only provides insight into cortical reactivity and effective connectivity but also enables pharmacological probing of inhibitory and excitatory circuits (Shafi et al., 2014).

Finally, rTMS protocols provide a means to study and induce synaptic plasticity in vivo. High-frequency rTMS, intermittent theta-burst stimulation (iTBS), and paired associative stimulation with a 25 ms interval (PAS25) typically produce long-term potentiation (LTP)-like effects, whereas low-frequency rTMS, continuous theta-burst stimulation (cTBS), and PAS10 are associated with long-term depression (LTD)-like effects (Chen et al., 2008; Huang et al., 2017; Lefaucheur, 2009; Suppa et al., 2017, 2016). These protocols can engage homosynaptic mechanisms, where repeated activation of the same synapses induces plasticity, or heterosynaptic mechanisms, where interactions between converging inputs drive changes in excitability (Ni et al., 2014). Plasticity responses are not fixed but vary across the lifespan (Freitas et al., 2011; Oberman and Benussi, 2023) and can be altered by systemic or neurological conditions (Fried et al., 2016; Tremblay et al., 2015). More recently, cortico-cortical paired associative protocols have been developed, in which stimulation of interconnected areas such as contralateral M1, premotor cortex, supplementary motor area, parietal cortex, or cerebellum is time-locked to M1 stimulation (Arai et al., 2011; Buch et al., 2010; Chao et al., 2015; Koch et al., 2013; Lu et al., 2012; Rizzo et al., 2009). These approaches offer novel opportunities to modulate inter-regional connectivity and plasticity, and thereby to gain deeper insight into distributed network dynamics.

3. Clinical applications of emergent neurophysiological techniques for early and differential diagnosis

3.1. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder of the human nervous system, characterised by dysfunction of the upper (UMN) and lower motor neurons (LMN) (Geevasinga et al., 2016c; Vucic et al., 2011, 2023). While focal disease onset is typical, evolution of disease ensues spreading to other body regions and resulting in global muscle wasting and weakness, with respiratory dysfunction representing the terminal phase of ALS (Dharmadasa et al., 2017; Vucic et al., 2014). Disease origin has been a long-standing debate, with three main hypotheses proposed: (i) dying forward hypothesis, whereby descending corticomotoneuronal tracts mediate LMN degeneration through an anterograde glutamatergic excitotoxic mechanism (Eisen et al., 2017, 1992), (ii) dying back hypothesis referring to a LMN onset-disease and secondary dysfunction of UMN pathways (Boillée et al., 2006; Fischer et al., 2004; Pun et al., 2006; Williamson and Cleveland, 1999), and (iii) independent degeneration and dysfunction of the upper and lower motor neurons occurring in a contiguous and random pattern (Ravits et al., 2007; Ravits and La Spada, 2009). Ultimately, the relationship between dysfunction of the upper and lower motor neurons is fundamental to diagnosis and understanding of ALS pathogenesis. The development of objective biomarkers of upper and lower motor neuron dysfunction has clarified ALS pathogenesis and introduced potential diagnostic and prognostic tools. These advances may also enable the identification of novel therapeutic targets, inform treatment strategies, improve patient stratification and monitoring in clinical ALS trials. Paired-pulse threshold tracking TMS has emerged as an important neurophysiological technique for assessing cortical excitability in neurological diseases with SICI and SICF exhibiting pathogenic and diagnostic utility in ALS (Vucic et al., 2023, 2013b; Vucic and Kiernan, 2017).

3.1.1. Pathogenic insights from threshold tracking TMS

Reduction or absence of SICI has been identified as an early and relatively specific feature in ALS (Blair et al., 2010; Hanajima et al., 1996; Menon et al., 2016, 2015; Suzuki et al., 2022; Tankisi et al., 2022; Vucic et al., 2008; Vucic and Kiernan, 2008, 2006; Zanette et al., 2002; Ziemann et al., 1997). Notably, this reduction may occur focally within the motor cortex during the first year of symptoms, paralleling the focal clinical onset of disease (Dharmadasa et al., 2020). Reduced SICI correlates with LMN dysfunction (Vucic and Kiernan, 2006), and may precede onset of LMN dysfunction in sporadic ALS (Menon et al., 2015). It has also been linked to specific ALS clinical features such as the split-hand and split-hand plus signs (Bae et al., 2014; Menon et al., 2014), disease evolution (Dharmadasa et al., 2020; Menon et al., 2017; Shibuya et al., 2017).

Abnormalities of SICI have also been reported in atypical ALS phenotypes including the flail arm and flail leg variants of ALS as well as primary lateral sclerosis (Geevasinga et al., 2015; Menon et al., 2016; Vucic and Kiernan, 2007). In familial ALS cohorts, reduction in SICI has been reported in phenotypes linked to mutations in the *superoxide dismutase-1* (Vucic et al., 2008), *fused in sarcoma* (Williams et al., 2013) and *C9orf72* genes (Nicholson et al., 2015). Importantly, asymptomatic mutation carriers exhibit normal cortical function (Nicholson et al., 2015), with SICI reduction preceding the clinical development of familial ALS by ~ 6 months (Vucic et al., 2008).

Reduced SICI has been proposed to reflect a compensatory response to peripheral neurodegeneration (Zanette et al., 2002). However, the observation of normal cortical excitability in ALS-mimic disorders (Menon et al., 2015; Vucic et al., 2010, 2008), together with the partial and transient normalization of SICI following treatment with the anti-glutamatergic agent riluzole (Geevasinga et al., 2016b; Vucic et al., 2013a), argues against a compensatory mechanism. Rather, dysfunction of GABAergic interneuronal circuits, acting via $GABA_A$ receptors, appears to be the most plausible mechanism for mediating SICI reduction in ALS, supported by pathological evidence in patients and mouse model (Clark et al., 2021; Foerster et al., 2012; Nihei et al., 1993; Y.-J. Zhang et al., 2016). Enhanced glutamatergic neurotransmission may also contribute to SICI reduction in (Geevasinga et al., 2016b; Vucic et al., 2013a). More recently, the reduction of SICI was reported to be more pronounced in ALS patients with absent or subtle UMN signs (Tankisi et al., 2022), raising questions about the pathogenic role of cortical hyperexcitability in typical ALS phenotypes. This result, however, is likely attributable to methodological differences, as the study employed a pseudorandom parallel ordering of ISIs rather than the conventional serial ascending approach, the latter demonstrating more robust distinctions in SICI between ALS and mimic disorders (Calma et al., 2025).

The physiological interpretation of SICI also depends on the orientation of the induced current and the specific I-wave components activated by TMS. Posterior-to-anterior currents preferentially recruit early I-waves (I1), whereas later I-waves (I2–I3) are more effectively elicited with lateral-to-medial stimulation (Hanajima et al., 1998). These differences are relevant to ALS pathophysiology, as alterations in I-wave composition or synchrony could contribute to the apparent reduction of SICI. Indeed, cortical hyperexcitability in ALS may reflect not only impaired GABAergic inhibition but also changes in the timing or relative contribution of I-wave volleys, which modify the net inhibitory-excitatory balance detected by paired-pulse TMS.

The reduction in SICI has been accompanied by an increase in SICF

(Van Den Bos et al., 2018; Santos Silva et al., 2025). This imbalance between inhibitory and facilitatory circuits can be quantified using the novel biomarker termed index of excitation, which is elevated in ALS and indicates that overactivity of facilitatory pathways contributes to cortical hyperexcitability. Importantly, this overactivity correlates with greater functional disability and the development of UMN signs, underscoring its pathogenic significance in ALS. More recently, dysfunction of distinct interneuronal circuits, preferentially activated by TMS in posterior-to-anterior and lateral-to-medial current directions, has been implicated in the development of cortical hyperexcitability in ALS (Pavey et al., 2024).

It may be argued that cortical hyperexcitability provides a unifying pathogenic framework for the apparent differences in patterns of disease spread in ALS, with hyperexcitability of specific corticomotoneuronal tracts acting as a conduit for propagation (Dharmadasa et al., 2024). A contiguous horizontal pattern of disease spread (limb-to-limb) is most frequently reported in ALS (Gargiulo-Monachelli et al., 2012; Korner et al., 2011; Menon et al., 2019), with concordance between UMN and LMN dysfunction in the affected region, as well as between the site of disease onset and limb dominance (Devine et al., 2014; Turner et al., 2011). Given the higher density of corticospinal tracts on the dominant side and their function in mediating complex finer tasks (Rose et al., 2012), the association between limb dominance and site of onset may be explained by greater corticomotoneuronal hyperexcitability in the corresponding region. The spread of disease to contiguous or non-contiguous regions could be explained by development of hyperexcitability in corticomotoneuronal pathways destined for specific body regions, resulting in a “river of hyperexcitability”. Support for this hypothesis is provided by threshold tracking TMS studies disclosing focal onset of cortical hyperexcitability within the M1 corresponding to site of disease onset (Dharmadasa et al., 2020; Menon et al., 2019).

Support for the pathogenic importance of cortical hyperexcitability has been provided by transgenic mouse model studies reporting that mislocalization of TDP-43 in the UMNs increases excitatory inputs to the spinal motor neurons and induces disease progression through a dying forward process (Reale et al., 2023). More recently, chronic cortical hyperexcitability was shown to induce cytoplasmic TDP-43 aggregation in upper and lower motor neurons, positioning hyperexcitability upstream of TDP-43 proteinopathy in ALS (Haidar et al., 2025). Collectively, the threshold tracking TMS findings support the concept of ALS being a multistep process (Al-Chalabi et al., 2014; Vucic et al., 2020, 2019), with cortical hyperexcitability representing a critical pathogenic step, perhaps mediated via a “dying-forward” process. For a summary of characteristic TMS findings see Table 1.

3.1.2. *Diagnostic utility of threshold tracking TMS*

At present, no pathognomonic test exists for ALS, and diagnosis still relies on the recognition of combined upper and lower motor neuron dysfunction using clinical and neurophysiological criteria, alongside exclusion of mimicking disorders (Brooks, 1994; Brooks et al., 2000; de Carvalho et al., 2008; Shefner et al., 2020). Over the past three decades, multiple diagnostic frameworks have been proposed to facilitate earlier and more reliable diagnosis and to support clinical trial recruitment. The most widely adopted include the clinically based El Escorial and revised El Escorial criteria, and the neurophysiologically integrated Awaji-Shima criteria (Brooks, 1994; Brooks et al., 2000; de Carvalho et al., 2008). However, these classifications are hindered by their reliance on multiple hierarchical levels of diagnostic certainty, their complexity, and limited inter-rater reproducibility. Critically, their sensitivity may be suboptimal, as they depend on disease progression and exclusion of mimicking disorders (Costa et al., 2012; Geevasinga et al., 2016a; Johnsen et al., 2019). More recently, the simplified Gold Coast criteria were proposed (Shefner et al., 2020), reducing diagnostic certainty to a single level defined by the presence of UMN and LMN dysfunction in one body region, or LMN dysfunction in two regions, in the context of disease progression and exclusion of mimicking disorders. Multiple studies across Europe (Ferullo et al., 2024; de Jongh et al., 2022; Pugdahl et al., 2021; Stikvoort García et al., 2023), North America (Jewett et al., 2022) and the Asia-Pacific (Ferullo et al., 2024; Hannaford et al., 2021; Otani et al., 2024; Shen et al., 2021) region, have consistently shown greater sensitivity of the Gold Coast criteria across ALS phenotypes, irrespective of site of onset, disease duration, or level of functional disability. Importantly, patients with predominantly lower motor neuron phenotypes (progressive muscular atrophy/flail arm variant) were appropriately captured, while those with primary lateral sclerosis were correctly excluded (Hannaford et al., 2021). Although the Gold Coast criteria generally outperform the revised El Escorial and Awaji criteria in terms of sensitivity, specificity remains variable, and inter-rater reproducibility has not yet been established. A fundamental limitation shared by all diagnostic frameworks is their dependence on the clinical detection of UMN dysfunction. In ALS, eliciting UMN signs can be challenging for several reasons (Swash, 2012), including: (i) extensive motor neuron loss; (ii) degeneration of spinal interneurons and gamma motor neurons; (iii) impaired descending excitatory motor input from propriospinal projections with consequent dysregulation of presynaptic inhibition and absent tendon reflexes; (iv) dispersion of efferent volleys due to distal

Table 1
Summary of characteristic TMS findings in neurological disorders.

Disease	RMT	AMT	CSP	SAI	SICI	ICF	SICF	LICI	LTP	LTD
ALS	=▼▲		▼	▼	▼	▲=	▲	▼		
AD	▼	▼	=	▼	=	=		=▼	▼	=
FTD	=		▼	=	▼	▼		▼	▼	▼
DLB				▼	▼	▼			▼	
PD	=▼		=▼	▼	▼	=▼	▲		▼	
PSP	=		▲	=▼	▼	=▼			▲	
CBS	▲		▼	=	▼	=▼▲			▼	

AD = Alzheimer’s disease; ALS = amyotrophic lateral sclerosis; AMT = active motor threshold; CBS = corticobasal syndrome; CSP = cortical silent period; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; ICF = intracortical facilitation; LICI = long-interval intracortical inhibition; LTD = long-term depression; LTP = long-term potentiation; PD = Parkinson’s disease; PSP = progressive supranuclear palsy; RMT = resting motor threshold; SAI = short-latency afferent inhibition; SICI = short-interval intracortical inhibition; SICF = short-interval intracortical facilitation; ▲ = increase; ▼ = decrease; = = no change.

axonal diameter changes causing asynchronous activation; and (v) disruption of spinal motor neuron and interneuronal networks, alongside disorganisation of alpha-gamma motor connectivity, producing variable spasticity and inconsistent release of primitive reflexes such as the Babinski sign.

The threshold tracking TMS technique provides an objective measure of UMN dysfunction in ALS, with SICI reduction being a robust diagnostic biomarker in ALS (Geevasinga et al., 2014; Menon et al., 2015; Vucic et al., 2011). Notably, SICI reduction reliably differentiates ALS from neuromuscular mimicking disorders, hastening the diagnosis of ALS by ~ eight months when compared to the revised El Escorial criteria (Vucic et al., 2011). Incorporating SICI into the Awaji criteria enhanced diagnostic sensitivity by 34 %, regardless of disease onset site or stage (Menon et al., 2015). Beyond typical presentations, threshold tracking TMS has enabled detection of subclinical UMN dysfunction, aiding diagnosis in atypical phenotypes (Menon et al., 2016; Tankisi et al., 2021; Tveit et al., 2023; Vucic and Kiernan, 2007). More recently, the threshold tracking TMS technique was shown to provide a measure of an imbalance between facilitatory and inhibitory circuit function, offering a reproducible biomarker of UMN dysfunction and thereby further aiding diagnosis (Santos Silva et al., 2025). Furthermore, the serial ascending threshold tracking paradigm demonstrated superior diagnostic performance compared to the parallel tracking approach, independent of disease stage, ALS phenotype, or degree of UMN involvement (Calma et al., 2025).

The principal limitation of threshold tracking TMS lies in its restricted accessibility, given the need for specialised hardware, software, and operator expertise. Until recently, its application has been largely confined to specialised centres. However, the recent commercialization of the technique is expected to lower these barriers, supporting its integration into both clinical practice and therapeutic trial settings (Vucic et al., 2025). To conclusively establish its diagnostic value, multicentre studies evaluating the sensitivity, specificity, and inter-rater reliability of threshold tracking TMS will be essential.

3.1.3. TMS-EEG

TMS-EEG is a novel neurophysiological approach that allows direct interrogation of cortical circuits in ALS, bypassing confounding influences from lower motor neurons (Tremblay et al., 2019). By capturing cortical responses in real time, TMS-EEG enables more detailed probing of discrete interneuronal dysfunction, thereby uncovering novel mechanisms of cortical hyperexcitability. In ALS, TMS-EEG has consistently revealed abnormalities in TEPs, particularly implicating GABAergic dysfunction and reinforcing the concept that cortical hyperexcitability arises from disinhibition (van den Bos et al., 2025). Single-pulse studies demonstrated a robust reduction in the N100 TEP component and pronounced variability of the N45, findings highly suggestive of impaired inhibitory function (van den Bos et al., 2025). Given pharmacological evidence that $GABA_A$- and $GABA_B$-mediated inhibition underpins the N45 and N100 potentials (Premoli et al., 2014), these abnormalities strongly point to dysfunction of cortical GABAergic neurotransmission in ALS. Further supporting this, paired-pulse paradigms have shown reduced inhibition of the P60 and N100 components, with the degree of N100 reduction correlating with longer disease duration (van den Bos et al., 2025).

Separately, paired-pulse TMS disclosed a significant increase in the P30 and P180 TEP components in ALS, while these components were not abnormal with single-pulse TMS-EEG studies. The precise mechanisms underlying the increase in P30 and P180 TEP components remains to be fully resolved, although a dysfunction across both facilitatory and inhibitory circuits has been suggested (van den Bos et al., 2025; Van Den Bos et al., 2018). This notion needs to be confirmed in future studies.

Emerging genetic and molecular evidence strongly implicates dysfunction of inhibitory GABAergic circuits in ALS, providing a mechanistic basis for the TMS-EEG abnormalities. Post-mortem studies have demonstrated degeneration of parvalbumin-positive interneurons (Maekawa et al., 2004; Nihei et al., 1993; W. Zhang et al., 2016), and reduced expression of mRNA $GABA_A$ receptor subunits in the primary motor cortex of ALS patients (Petri et al., 2003). Complementing these findings, PET studies using ^{11}C-flumazenil have shown in $GABA_A$ receptor binding in ALS (Turner et al., 2005; Wicks et al., 2008; Yabe et al., 2012). At the genetic level, polygenic risk analyses have consistently mapped ALS susceptibility to GABAergic interneurons and oligodendrocytes (Saez-Atienzar et al., 2021). Converging evidence from transgenic mouse models further underscores the pathogenic role of interneuronal dysfunction: selective inhibition of parvalbumin-positive interneurons induces cortical hyperexcitability (W. Zhang et al., 2016), whereas restoring their function delays disease onset and prolongs survival (Khademullah et al., 2020). Taken together, these data highlight GABAergic circuit degeneration as a central contributor to ALS pathophysiology and suggest that therapeutic strategies aimed at restoring cortical inhibition could hold significant promise.

The potential advantage of TMS-EEG compared to conventional TMS-EMG measures of cortical inhibitory neuronal function is that it directly assesses cortical activity, effectively bypassing contributions from the brainstem and spinal cord. TMS-EEG also enables assessment of cortical function in the setting of marked muscle wasting that precludes reliable recording of MEPs. Although TMS-EEG is technically more demanding than TMS-EMG, recent technological advances, such as faster and more precise TEP acquisition, improved signal fidelity, and automated online processing, are paving the way for its clinical translation. These developments will allow TMS-EEG to be applied as a biomarker of target engagement and therapeutic efficacy in upcoming clinical trials (Kiernan et al., 2021). Collectively, TMS-EEG has emerged as a promising tool to detect cortical hyperexcitability and dissect inhibitory circuit dysfunction in ALS, with the added potential to serve as a reliable outcome measure in future clinical trials.

3.2. Cognitive decline and dementia

3.2.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia (Scheltens et al., 2021, 2016), clinically characterized by progressive amnestic impairment and additional cognitive deficits that interfere with daily functioning (Knopman et al., 2021). The pathological hallmarks of AD include extracellular amyloid-β plaques and intraneuronal tau neurofibrillary tangles, with atrophy beginning in the entorhinal cortex and spreading to limbic, paralimbic, and finally associative neocortical areas (Knopman et al., 2021). Although widespread cortical atrophy is typically observed in later stages, alterations in functional connectivity are already evident in prodromal phases (Brier et al., 2012; Dennis and Thompson, 2014; Ferreri et al., 2003). In this context, TMS provides a unique opportunity to probe cortical excitability, connectivity, and plasticity in vivo, offering insight into pathophysiological mechanisms and potential biomarkers for early and differential diagnosis (Di Lazzaro et al., 2021).

3.2.1.1. Pathogenic insights from single and paired-pulse TMS. A consistent finding in AD is increased cortical excitability, most commonly reflected by reductions in RMT (Alagona et al., 2004; Brem et al., 2013; de Carvalho et al., 1997; Ferreri et al., 2011; Hoeppner et al., 2012; Inghilleri et al., 2006; Issac et al., 2013; Khedr et al., 2011; Di Lazzaro et al., 2008, 2004; Di Lorenzo et al., 2013; Martorana et al., 2009, 2008; Motta et al., 2018; Schirinzi et al., 2018; Terranova et al., 2013; Trebbastoni et al., 2012; Wang et al., 2016), and in several studies, active motor threshold (AMT) (Khedr et al., 2011; Di Lazzaro et al., 2007a; Pepin et al., 1999; Wegrzyn et al., 2013). These findings likely reflect imbalances in GABAergic, glutamatergic, and cholinergic neurotransmission within M1. Since TMS drives high-frequency discharges of pyramidal neurons, enhanced non-NMDA receptor activity has been proposed as a contributing mechanism (Brem et al., 2013; Di Lazzaro

et al., 2004). Importantly, motor cortex hyperexcitability does not appear to correlate directly with structural degeneration of corticospinal or callosal tracts (Wegrzyn et al., 2013) or with local cortical thickness (Niskanen et al., 2011) suggesting that functional alterations may precede or occur independently of atrophy.

Regarding inhibitory circuits, $GABA_A$-mediated inhibition as measured by SICI has often been reported to be preserved (Alberici et al., 2008; Benussi et al., 2018b, 2018a, 2017a; Di Lazzaro et al., 2008, 2007a, 2004, 2002b; 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 several studies have shown a reduction in SICI (Hoeppner et al., 2012; Liepert et al., 2001; Martorana et al., 2008; Nardone et al., 2006; Olazarán et al., 2010; Pierantozzi et al., 2004). A *meta*-analysis suggests that SICI impairment may become more evident with longer disease duration, consistent with a stage-dependent phenomenon (Mimura et al., 2021). $GABA_B$-mediated inhibition, assessed by cortical silent period (CSP), is largely unchanged (Alagona et al., 2004; Inghilleri et al., 2006; Issac et al., 2013; Di Lazzaro et al., 2002b; Liepert et al., 2001; Trebbastoni et al., 2012), although long-interval intracortical inhibition (LICI) has been reported to be reduced in some studies (Benussi et al., 2020e, 2017b; Brem et al., 2013). Intracortical facilitation (ICF), reflecting glutamatergic circuit function, tends to be diminished across multiple cohorts (Alberici et al., 2008; Benussi et al., 2020e, 2018a, 2017b; Liepert et al., 2001; Di Lorenzo et al., 2013; Martorana et al., 2013; Motta et al., 2018; Nardone et al., 2008, 2006; Olazarán et al., 2010).

Given the pivotal role of cholinergic dysfunction in AD, SAI has been extensively investigated and is consistently reduced (Bella et al., 2016; Benussi et al., 2021a, 2022b, 2022a, 2020e, 2018a, 2017b; Bracca et al., 2023; Hwang et al., 2018; Koch et al., 2016; Di Lorenzo et al., 2013; Motta et al., 2018; Nardone et al., 2014b; Schirinzi et al., 2018; Yildiz et al., 2018). Importantly, SAI abnormalities can be acutely normalized by acetylcholinesterase inhibitors, L-dopa, or dopamine agonists (Koch et al., 2014; Di Lazzaro et al., 2004; Martorana et al., 2013, 2009; Nardone et al., 2014a), and are enhanced by cerebellar cTBS, suggesting additional cerebellar involvement (Di Lorenzo et al., 2013). Taken together, these findings indicate that SICI and ICF are relatively preserved, while SAI is consistently impaired in AD (Mimura et al., 2021).

3.2.1.2. Cortical plasticity. Synaptic degeneration is a central driver of cognitive decline in AD (Walsh et al., 2002). Preclinical data indicate that soluble amyloid-β oligomers disrupt long-term potentiation (LTP) and promote long-term depression (LTD) (Li et al., 2009; Shankar et al., 2008), facilitating tau-mediated synaptic toxicity (Palop and Mucke, 2010). In humans, intermittent theta-burst stimulation (iTBS) is widely used to probe cortical plasticity, producing LTP-like increases in excitability via NMDA/AMPA mechanisms (Huang et al., 2005). AD patients exhibit impaired LTP-like plasticity, often with paradoxical LTD-like responses, together with impaired SAI (Koch et al., 2012; Di Lorenzo et al., 2016). These abnormalities correlate selectively with memory performance (Di Lorenzo et al., 2018), discriminate AD from controls with high diagnostic accuracy (Motta et al., 2018), and predict faster cognitive decline. Plasticity alterations are further linked to higher CSF tau levels, which are associated with a shift from LTP-like to LTD-like cortical responses and faster cognitive decline (Koch et al., 2016) and this relationship is strongly modulated by *APOE* genotype, being present only in *APOE ε4* carriers (Koch et al., 2017). Consistent with these findings, a subsequent study demonstrated that QPS5-induced LTP-like plasticity correlates with both amyloid and tau biomarkers as well as cognitive performance in the same individuals, suggesting that abnormal motor-cortical plasticity may serve as an early neurophysiological biomarker of Alzheimer's disease pathology and follow a progression pattern similar to that of other established biomarkers (Murakami et al., 2024). Methodological rigor is critical as plasticity measures show variable test–retest reliability depending on stimulation parameters (Davila-Pérez et al., 2018; Schilberg et al., 2017; Vernet et al., 2014; Ziemann and Siebner, 2015) For a summary of characteristic TMS findings see Table 1.

3.2.1.3. Cortico-cortical connectivity and TMS-EEG. Alterations in cortico-cortical connectivity are increasingly recognized as a hallmark of Alzheimer's disease. Interhemispheric connectivity assessed by the ipsilateral silent period (iSP) is consistently abnormal, with prolonged latency or duration reflecting impaired transcallosal inhibition and correlating with cognitive severity (Hoeppner et al., 2012; Khedr et al., 2011; Wegrzyn et al., 2013). Similarly, effective connectivity between posterior parietal cortex and M1 is disrupted, requiring stronger conditioning and longer intervals to induce facilitation, and these abnormalities correlate with episodic memory and executive dysfunction (Bonnì et al., 2013).

TMS-EEG has extended these insights by directly probing large-scale network dynamics. Stimulation of frontal cortex reveals abnormal propagation of TMS-evoked activity, indicating both impaired local excitability and reduced long-range spread (Casarotto et al., 2011). In line with early sensorimotor involvement in Alzheimer's disease, TMS-EEG studies have shown that the P30 component, originating mainly from parietal and premotor regions, is already altered in prodromal and early stages of the disease. Specifically, patients with MCI and early AD exhibit a reduction of P30 amplitude over M1 and connected parietal areas, reflecting impaired cortico-cortical connectivity and early network dysfunction (Ferreri et al., 2016; Julkunen et al., 2008, 2011). Moreover, source-localized analyses have demonstrated that P30 amplitude systematically decreases as cognitive impairment worsens, closely tracking Mini-Mental State Examination scores and disease severity, thus providing a direct physiological marker of disease progression (Bagattini et al., 2019).

Oscillatory responses to TMS-EEG provide further pathophysiological information. Reduced frontal gamma activity has been consistently observed in mild-to-moderate AD, and lower gamma predicted impaired LTP-like plasticity and accelerated cognitive decline over 24 weeks (Casula et al., 2023, 2022; Maiella et al., 2024). Longitudinal work in amnestic mild cognitive impairment (MCI) showed that reduced intertrial coherence in beta and gamma bands over M1 differentiated converters to AD from non-converters, while metrics of waveform stability improved individual-level prediction (Ferreri et al., 2021). Beyond patient cohorts, perturbation-based indices of cortical excitability obtained with TMS-EEG correlate strongly with plasma p-tau181 in cognitively unimpaired adults, outperforming spontaneous EEG markers and supporting a mechanistic link between excitability and tau-related pathology in preclinical stages (Perellón-Alfonso et al., 2024).

Importantly, TMS-EEG can also be used to track treatment engagement and guide network-targeted interventions. High-frequency rTMS of the precuneus was shown to strengthen precuneus-medial frontal coupling and enhance parietal beta/gamma oscillations. In a randomized, double-blind, sham-controlled trial, precuneus stimulation stabilized cognitive outcomes and preserved precuneus excitability with concomitant enhancement of local gamma activity (Koch et al., 2025, 2022).

Finally, multimodal studies are beginning to link TMS-EEG metrics with underlying neurotransmission. In healthy individuals, 7 T magnetic resonance spectroscopy demonstrated that cortical GABA concentrations relate most strongly to model-derived indices of tonic inhibition inferred from TEPs, providing a mechanistic bridge between inhibitory tone and perturbation-based EEG measures (Paparella et al., 2025). Although not yet applied systematically in AD, these findings reinforce the interpretability of inhibitory TEP components, which are frequently reported as abnormal in AD cohorts.

3.2.2. Frontotemporal lobar degeneration

Frontotemporal dementia (FTD) is one of the most frequent

neurodegenerative dementias after Alzheimer's disease, clinically characterized by behavioural change, language impairment, and executive dysfunction (Grossman et al., 2023). Three main variants are recognized: the behavioural variant (bvFTD) (Rascovsky et al., 2011) and the agrammatic and semantic variants of primary progressive aphasia (avPPA, svPPA) (Gorno-Tempini et al., 2011). Frontotemporal lobar degeneration (FTLD) selectively targets frontal and temporal cortices, with tau or TAR DNA-binding protein 43 (TDP-43) pathology as predominant hallmarks (Neumann and Mackenzie, 2019; Spillantini and Goedert, 2013). Genetic mutations account for ~ 10–30 % of cases, most commonly in *MAPT* and *GRN*, or a hexanucleotide repeat expansion in *C9orf72* (Benussi et al., 2015; Borroni and Benussi, 2019). Converging evidence indicates prominent alterations of GABAergic and glutamatergic transmission, with relative sparing of cholinergic systems (Benussi et al., 2019a; Borroni et al., 2018; Murley et al., 2020; Murley and Rowe, 2018).

3.2.2.1. Pathogenic insights from single and paired-pulse TMS. TMS has revealed several motor system abnormalities in FTD, including reduced or absent MEPs, prolonged MEP latencies, and increased central motor conduction time (CMCT) (Bae et al., 2016; Burrell et al., 2011; Chandra et al., 2016; Di Lazzaro et al., 2006; Schanz et al., 2016; Wang et al., 2016). In contrast to AD, resting motor threshold (RMT) is generally unchanged (Alberici et al., 2008; Bae et al., 2016; Benussi et al., 2019d, 2019b, 2018a, 2017b; Burrell et al., 2011; Chandra et al., 2016; Issac et al., 2013; Di Lazzaro et al., 2006; Pierantozzi et al., 2004; Di Stasio et al., 2018; Wang et al., 2016).

Early small studies reported no major differences in SICI or ICF (Alberici et al., 2008; Pierantozzi et al., 2004), but subsequent larger cohorts consistently demonstrated reductions in both SICI and ICF (Bae et al., 2016; Benussi et al., 2022b, 2020d, 2020b, 2020g, 2020c, 2020e, 2019d, 2018a, 2018b, 2017a, 2017b; Bracca et al., 2023; Burrell et al., 2011; Gazzina et al., 2018; Italia et al., 2024; Padovani et al., 2019, 2018; Palese et al., 2020), in keeping with FTLD-related inhibitory and excitatory dysfunction (Benussi et al., 2021; Murley and Rowe, 2018). By contrast, SAI is typically normal (Benussi et al., 2020e, 2018a, 2017a, 2017b; Di Lazzaro et al., 2006; Padovani et al., 2018), supporting the view that cholinergic deficits are not a core feature of FTD.

Neurophysiology-phenotype correlations underscore clinical relevance: reduced SICI and LICI correlate with "positive" behavioural symptoms (restlessness, irritability, aggression), whereas diminished ICF relates to "negative" symptoms (apathy, aspontaneity, indifference) (Benussi et al., 2020b). This pattern aligns with models hypothesizing that disinhibition of cortical circuits drives positive symptoms, while loss of excitatory drive contributes to negative symptoms (Benussi et al., 2019a).

Importantly, similar abnormalities are present in genetic FTD, including presymptomatic mutation carriers (Benussi et al., 2019d, 2016; Gazzina et al., 2018). Deficits in SICI and ICF can precede the estimated clinical onset by more than three decades, with structural atrophy and cognitive decline emerging later (Benussi et al., 2019d). In presymptomatic *GRN* carriers, reduced ICF correlates with cortical thinning and reduced surface area of the right insula, pointing to early glutamatergic disruption within salience network hubs (Gazzina et al., 2018). Moreover, SICI, ICF, and LICI correlate with disease severity, and SICI best predicts clinical progression, explaining ~ 72.5 % of the variance in FTLD-modified Clinical Dementia Rating scale (FTLD-CDR) change over 12 months (Benussi et al., 2020c).

Recent studies have linked these neurophysiological changes to fluid biomarkers of disease. In a large multicenter cohort of 406 individuals, serum GFAP, a marker of astroglial activation, was significantly elevated in FTD and correlated with cognitive impairment and disease severity (Benussi et al., 2020a). Importantly, higher GFAP levels were associated with greater impairment in LICI, suggesting a direct relationship between astrocytic pathology and $GABA_B$-mediated cortical inhibition. These associations were independent of CSF tau and amyloid biomarkers, emphasizing their specificity for non-Alzheimer's disease mechanisms (Benussi et al., 2020a).

Additional work has shown that serum neurofilament light (NfL) levels, a marker of axonal degeneration, were strongly correlated with impairment of GABAergic circuits, as reflected by reductions in SICI and LICI, but not with glutamatergic or cholinergic measures (Benussi et al., 2020f). Higher NfL levels were associated with more severe clinical symptoms and greater frontotemporal atrophy, underscoring its role as a marker of disease burden. In contrast, serum p-Tau_{181} levels were not associated with TMS measures in FTD, although they correlated with SAI in AD, reflecting cholinergic deficits specific to Alzheimer's pathology.

3.2.2.2. Cortical plasticity. LTP- and LTD-like plasticity are impaired in FTD across stages. Facilitatory sensorimotor PAS reveals reduced LTP-like responses in both presymptomatic and symptomatic individuals (Benussi et al., 2016). Using theta-burst stimulation, deficits are evident for iTBS (LTP-like) and cTBS (LTD-like), with greater impairment in patients without associated parkinsonism compared with those with parkinsonism (Di Stasio et al., 2018). These human data mirror animal models, where synaptic plasticity deficits are detectable before overt neuropathology (e.g., *GRN* knockout mice) (Petkau et al., 2012) For a summary of characteristic TMS findings see Table 1.

3.2.2.3. TMS-EEG. TMS-EEG applications, though much fewer than in AD, provide direct evidence of abnormal cortical reactivity and oscillatory dynamics in bvFTD. In particular, a recent study demonstrated that treatment with ultramicronized palmitoylethanolamide combined with luteolin (PEA-LUT) was associated with improved frontal lobe functions and a concomitant increase in TMS-evoked high-frequency (beta-gamma) activity over prefrontal regions, supporting both impaired frontal oscillatory responses in bvFTD and their potential pharmacological modulation (Assogna et al., 2020). While findings are still preliminary, these measures show promise as biomarkers for disease mechanisms and as tools to monitor treatment effects.

3.2.3. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia after AD and is characterized clinically by fluctuating cognition, parkinsonism, REM sleep behaviour disorder, and recurrent complex visual hallucinations (McKeith et al., 2017). Neuropathologically, DLB is defined by widespread cortical and subcortical deposition of α-synuclein in the form of Lewy bodies and Lewy neurites, frequently accompanied by concomitant Alzheimer-type pathology. Cholinergic dysfunction is generally more severe in DLB than in AD, while glutamatergic and GABAergic alterations also contribute to symptomatology (Khundakar et al., 2016; Okkels et al., 2024).

3.2.3.1. Pathogenic insights from paired-pulse TMS. The majority of TMS studies in DLB have used canonical paired-pulse protocols probing intracortical inhibition and facilitation. Findings for SICI are inconsistent: some studies reported no differences compared to AD or controls (Di Lazzaro et al., 2007b; Nardone et al., 2006), while others demonstrated reduced SICI in DLB patients (Benussi et al., 2021b, 2022c, 2020e, 2018b; Rizzardi et al., 2025). ICF has also been found to be diminished in several studies, again reflecting excitatory dysfunction (Benussi et al., 2021b; Benussi et al., 2022c, 2020e, 2018b; Rizzardi et al., 2025).

Given the profound cholinergic deficit in DLB, SAI has been studied more extensively. Several groups found reduced SAI compared with controls (Benussi et al., 2022c, 2020e, 2018b; Di Lazzaro et al., 2007b; Marra et al., 2012; Padovani et al., 2019; Rizzardi et al., 2025), although others reported preserved SAI in DLB with impairment seen only in AD (Nardone et al., 2006). Notably, SAI correlates with severity of visual hallucinations in DLB (Marra et al., 2012), aligning with the role of

cholinergic deficits in the genesis of this symptom (Esmaeeli et al., 2019).

3.2.3.2. Cortical plasticity. Direct evidence on cortical plasticity in DLB has only recently emerged. Earlier work lacked consistent data from PAS or TBS paradigms, and conclusions relied mainly on neuropathological and preclinical studies suggesting that α-synuclein aggregates interfere with synaptic function and plasticity (Schulz-Schaeffer, 2010). A recent comparative TMS study provided the first direct evidence of plasticity impairment in DLB (Olğun et al., 2024). Using intermittent iTBS, patients with DLB showed a marked reduction in LTP-like plasticity, reflected by diminished MEP facilitation after stimulation compared to healthy controls For a summary of characteristic TMS findings see Table 1.

3.2.3.3. TMS-EEG. TMS-EEG applications in DLB are still limited, but recent work has begun to reveal network-level dysfunctions underlying core symptoms. Spontaneous EEG consistently shows posterior slowing (Bonanni et al., 2015; Schumacher et al., 2019), and perturbation-based approaches can help disentangle whether these changes reflect altered excitability or impaired connectivity. A recent study directly examined effective connectivity within the visual (VIS) and dorsal attention (DAN) networks in Lewy body diseases. TMS-EEG of the intraparietal sulcus and frontal eye fields, key DAN nodes, showed reduced evoked activity in patients with visual hallucinations, including those with DLB, whereas stimulation of early visual cortex (V1/V2) elicited preserved responses. These results suggest that hallucinations stem from impaired top-down attentional control rather than bottom-up visual dysfunction (Leodori et al., 2023).

3.2.4. Diagnostic utility of TMS and TMS-EEG in the differential diagnosis of cognitive decline and dementia

Validated imaging and fluid biomarkers are widely used in the diagnostic work-up of dementia and show high accuracy, but their utility is limited by cost, invasiveness, and restricted applicability across different dementia subtypes (Frisoni et al., 2017). Blood-based biomarkers have shown great potential but are still not widely applied on clinical grounds (Benussi et al., 2025; Teunissen et al., 2022). In contrast, TMS offers a non-invasive and accessible approach, and several studies have demonstrated its diagnostic potential in distinguishing among AD, DLB, and FTD.

In a multicentre study of 175 participants, the ratio between SICI-ICF and SAI (SICI/ICF divided by SAI) differentiated FTD from AD with 91.8 % sensitivity and 88.6 % specificity, AD from controls with 84.8 % sensitivity and 90.6 % specificity, and FTD from controls with 90.2 % sensitivity and 78.1 % specificity (Benussi et al., 2017b). Subsequent studies confirmed that adding TMS to routine clinical evaluation significantly increased diagnostic confidence in distinguishing AD from FTD, with an effect comparable to established amyloid biomarkers (Benussi et al., 2018a).

TMS has also proven effective in the MCI stage. In single-centre cohorts, TMS reached ~ 90 % accuracy in discriminating MCI due to AD from non-AD MCI, again improving diagnostic confidence to a degree comparable with amyloid biomarkers (Padovani et al., 2019).

A more recent multicentre study including 694 participants (273 CE, 67 DLB, 207 FTD, 147 controls) applied machine learning to TMS measures (SICI, ICF, SAI, LICI) and achieved very high diagnostic accuracy (AUC 0.89–0.92) across groups (Benussi et al., 2020e). The classifier followed a hierarchical approach: (i) controls versus patients, (ii) FTD versus central cholinergic dementias (AD, DLB), and (iii) AD versus DLB. Importantly, the large sample size allowed for robust cross-validation, minimizing overfitting, and the authors released an open-access R script enabling classification of individual patients from raw TMS indices.

Using the same framework, the group extended their work to prodromal disease also from a multicentre cohort. A classifier trained on TMS measures differentiated MCI-AD, MCI-FTD, and MCI-DLB with high accuracy (AUC 0.72–0.86) and precision (0.72–0.90) (Benussi et al., 2021b).

Recent evidence demonstrated that combining TMS measures with blood-based biomarkers further increases diagnostic power. In a cohort of 202 individuals, the best model for identifying dementia cases from healthy controls included both plasma markers (p-Tau_{181}, GFAP, NfL) and TMS indices (SICI, ICF, SAI), yielding an AUC of 0.99. Similarly, for differentiating AD from FTD, combining plasma p-Tau_{181}, $A\beta_{42/40}$ ratio, SICI, ICF, and SAI achieved an AUC of 0.98. Notably, while SAI alone was the best single discriminator for AD versus FTD (AUC 0.96), combining blood and neurophysiological measures provided additional robustness and clinical interpretability (Benussi et al., 2022b).

Beyond motor-based paradigms, recent studies have explored the diagnostic potential of TMS-EEG in dementia. TMS-EEG has emerged as a promising tool for differential diagnosis in dementia by directly probing cortical reactivity and network-level dynamics. Several recent studies have evaluated its diagnostic accuracy using different analytic frameworks.

Single-pulse TMS-EEG over the left dorsolateral prefrontal cortex combined with machine learning has demonstrated high accuracy in distinguishing AD from controls. By extracting more than 150 time-domain features, including post-TMS maximum amplitude, Hjorth complexity, and TEP amplitude in the 45–80 ms window, a Random Forest classifier trained with leave-one-subject-out validation achieved 92.9 % accuracy, 96.2 % sensitivity, and 87.9 % specificity, indicating that both local cortical reactivity and distributed responses carry diagnostic value (Tăuţan et al., 2023).

Energy-based perturbation metrics have also been proposed to quantify the amplitude and duration of TMS-evoked responses, reflecting the time required for the EEG signal to return to baseline. In a cohort of AD patients and controls, three indices, including the Target Engagement Duration Index, the Engagement Decay Index, and the Target Engagement Index, achieved 69.3 % accuracy (72.2 % sensitivity, 66.4 % specificity), with the most reliable results obtained using a 20 ms sliding window. Although less accurate than feature-rich models, these indices provide a direct summary of perturbational recovery dynamics and may complement other markers (Tautan et al., 2022).

An alternative approach based on multivariate empirical mode decomposition (MEMD) has characterized the oscillatory structure of TMS-evoked activity. Compared with controls, AD patients exhibited a weakened slow-frequency response and a reduced biphasic pattern in faster modes. Classification based on these features achieved robust discrimination, with true- and false-positive rates of 85 % and 23 %, respectively (Bernardi et al., 2025).

Finally, a spatiotemporal analysis of canonical TEP components demonstrated that features of the N100 and P200 extracted from predefined frontal and parietal regions of interest can reliably separate cognitively impaired individuals from controls. Classification based on N100 time-domain features reached 88.4 % accuracy, with right frontal and left parietal regions providing the strongest contribution, underscoring the diagnostic value of canonical TEP markers (Zhang et al., 2021).

Taken together, these findings demonstrate that TMS and TMS-EEG provide robust, non-invasive biomarkers capable of differentiating between major dementia subtypes and identifying prodromal disease. Their integration into clinical workflows has the potential to complement established imaging and fluid markers, broadening access to early and accurate diagnosis.

3.3. Movement disorders

3.3.1. Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting ~ 1 % of individuals older than 65 years

(Bloem et al., 2021). Clinically, PD is characterized by bradykinesia, rigidity, and resting tremor, with heterogeneous motor subtypes (tremor-dominant vs. akinetic-rigid) and frequent non-motor manifestations. Pathophysiologically, degeneration of dopaminergic neurons in the substantia nigra and dysfunction of basal ganglia-cortical circuits result in abnormal motor control. Given its ability to probe cortical excitability and plasticity, TMS has been widely applied to study PD pathophysiology and treatment effects (Suppa et al., 2025).

3.3.1.1. Pathogenic insights from paired-pulse TMS. Motor threshold findings in PD are heterogeneous. Most studies report normal RMT and AMT (Chen and Rothwell, 2012), but some describe reduced RMT in patients with marked rigidity (Cantello et al., 1991; Spagnolo et al., 2013; Tremblay and Tremblay, 2002; Valls-Solé et al., 1994). In contrast, AMT has occasionally been found to be increased and associated with bradykinesia (Ellaway et al., 1995), albeit this relationship is not consistently observed (Bologna et al., 2018). Tremor-dominant patients may exhibit lower RMT and AMT compared with akinetic-rigid subtypes and controls (Khedr et al., 2021). Recruitment curve slopes are often steeper at rest but flatter during contraction, correlating with bradykinesia severity and disease stage (Bologna et al., 2018; Valls-Solé et al., 1994), consistent with compensatory hyperexcitability.

Inhibitory circuits are also abnormal in PD. SICI is frequently reduced (Ni et al., 2013; Ridding et al., 1995), including on the less affected side of de novo patients (Ammann et al., 2021), and declines further with disease progression (Kojovic et al., 2015). Reports of normalization with levodopa (Ni et al., 2013; Ridding et al., 1995) or subthalamic nucleus deep brain stimulation (Cunic et al., 2002) contrast with negative findings (Bologna et al., 2018; Lewis and Byblow, 2002; MacKinnon et al., 2005), likely reflecting clinical heterogeneity. CSP duration, another $GABA_B$-mediated marker, is variably reduced (Cantello, 2002), shorter in the "off" than "on" state but often not different from controls (Ridding et al., 1995). LICI findings are inconsistent, with reductions (Chu et al., 2009), increases (Berardelli et al., 1996), and normal results (Sailer et al., 2003; Valzania et al., 1997), reflecting methodological differences. Recent evidence has demonstrated that SICI reduction is present across the spectrum of alpha-synucleinopathies, being detectable in drug-naïve PD patients, more pronounced in DLB, and milder in individuals with idiopathic REM sleep behaviour disorder (iRBD). This pattern suggests a progressive gradient of cortical disinhibition, with early involvement occurring before the onset of motor symptoms and worsening as the disease advances (Rizzardi et al., 2025).

Facilitatory measures also reveal circuit dysfunction. ICF is variably normal (Ridding et al., 1995), reduced (Bareš et al., 2003), or increased (Lefaucheur et al., 2004). Recent evidence indicates that ICF is slightly reduced in PD compared to controls, with more pronounced reductions observed in DLB. In iRBD, ICF values are more variable, suggesting that early glutamatergic dysfunction may precede conversion to DLB rather than PD (Rizzardi et al., 2025). In contrast, SICF is consistently enhanced, even in de novo PD patients (Shirota et al., 2019), and inversely correlates with SICI (Ni et al., 2013). SICF is further elevated in dyskinetic patients (Guerra et al., 2019). Triple-pulse protocols indicate altered SICI-SICF interactions, with absent modulation in PD compared to controls, particularly in patients with greater motor impairment; levodopa may normalize these effects (Saravanamuttu et al., 2021). Notably, SICI depends on the direction of the induced current and the pattern of I-wave recruitment. When assessed using posterior-to-anterior currents, SICI is typically reduced in PD, whereas it may be preserved with anterior-to-posterior stimulation, suggesting differential engagement of inhibitory interneurons and possible alterations in I-wave composition (Hanajima et al., 2011). These findings point to abnormal interactions between inhibitory and facilitatory circuits, dependent on disease stage and phenotype.

As the disease progresses beyond motor symptoms, other neurotransmitter systems become involved, contributing to cognitive and non-motor manifestations. Among these, cholinergic dysfunction plays a pivotal role and can be assessed in vivo using SAI. Cognitive decline typically emerges in later PD stages, paralleling the spread of Lewy body pathology to cortical regions (Postuma et al., 2018). Early deficits often involve executive and visuospatial domains, progressing to broader cognitive dysfunction. Reduced SAI has been consistently linked to cognitive impairment in PD (Celebi et al., 2012; Dubbioso et al., 2019; Nardone et al., 2013; Yarnall et al., 2013), and predicts risk of dementia, visual hallucinations (Manganelli et al., 2009), dysphagia (Lee et al., 2015), olfactory dysfunction (Oh et al., 2017; Versace et al., 2017), and REM sleep behaviour disorder (Nardone et al., 2013). In drug-naïve PD, SAI is generally preserved, while mild reductions are observed in individuals with idiopathic REM sleep behaviour disorder and marked impairments are seen in those with DLB, suggesting a progressive gradient of cholinergic involvement across the alpha-synucleinopathy spectrum (Rizzardi et al., 2025). Conversely, stronger SAI in medicated patients correlates with better gait performance (Rochester et al., 2012), while reduced SAI is associated with gait instability and falls (Pelosin et al., 2016). Together, these findings indicate that progressive cholinergic degeneration may underline both cognitive and motor complications in the spectrum of alpha-synucleinopathies.

3.3.1.2. Cortical plasticity. Cortical plasticity is consistently impaired in PD. Unlike healthy controls, PD patients often fail to exhibit facilitation after HF-rTMS (Gilio et al., 2002) or inhibition after LF-rTMS (Lefaucheur et al., 2004). PAS protocols reveal absent or blunted LTP-like plasticity (Bologna et al., 2018; Kojovic et al., 2012; Morgante et al., 2006; Ueki et al., 2006). Levodopa may restore PAS-induced plasticity in non-dyskinetic patients but not in those with dyskinesias (Morgante et al., 2006; Ueki et al., 2006), suggesting dopaminergic state and motor complications modulate plasticity. In line with these findings, quadripulse stimulation (QPS5) studies have demonstrated reduced LTP-like plasticity in early-stage PD, which can be restored by levodopa and shows an inverse correlation with motor symptom severity, particularly bradykinesia and rigidity affecting the upper limbs (Moriyasu et al., 2022). For a summary of characteristic TMS findings see Table 1.

3.3.1.3. Cortico-cortical connectivity and TMS-EEG. Interhemispheric and cortico-cortical connectivity are also disrupted in PD. Callosal inhibition is altered, with reduced LIHI in patients with mirror movements, while SIHI may remain intact (Li et al., 2007). Tremor-dominant subtypes show shorter iSP duration, while akinetic-rigid patients exhibit longer latency relative to controls (Khedr et al., 2021).

Cerebellar inhibition (CBI) indexes the cerebello-thalamo-cortical pathway and is typically assessed with a conditioning TMS pulse over the cerebellum followed by an M1 test pulse at interstimulus intervals (ISIs) of ~ 5–8 ms (Pinto and Chen, 2001; Ugawa et al., 1995). Cerebellar-cortical interactions are impaired as reflected by reduced CBI, which may normalize with dopaminergic treatment in some cohorts (Ni et al., 2010; Shirota et al., 2010) but not others (Carrillo et al., 2013).

TMS-EEG studies in PD have revealed consistent alterations in cortical excitability, propagation, and oscillatory dynamics. In advanced PD with STN-DBS, cortical reactivity is modulated in a treatment-specific manner, with DBS enhancing early TEPs and high-alpha oscillations and levodopa augmenting later components and beta power (Casula et al., 2017). Region-specific abnormalities include reduced M1 P30 and increased pre-SMA N40, both dopamine-sensitive, with M1 hypoexcitability already detectable in de novo PD (Leodori et al., 2024). Broader mapping indicates reduced waveform adherence, increased variability, and weaker interhemispheric connectivity in motor and prefrontal circuits (Maidan et al., 2021), while occipital stimulation shows reduced interhemispheric coupling that classifies rapid progressors with high accuracy (Zifman et al., 2024). Symptom-specific

effects are also evident: re-emergent tremor is linked to M1 as a causal node, with TMS resetting tremor and P60 dynamically tracking tremor expression (Leodori et al., 2020). Levodopa increases SMA excitability in relation to nigrostriatal dopaminergic deficits (Casarotto et al., 2019), and DBS conditioning paradigms reveal GABAergic inhibitory projections mediating normalization of cortical responses (Passera et al., 2023). More recently, perturbation of M1 and DLPFC demonstrated abnormal P30/P60 amplitudes and reduced alpha/beta power, with M1 excitability correlating with motor severity and DLPFC measures relating to depressive symptoms (Zhu et al., 2025). Collectively, these findings highlight early M1 hypoexcitability, compensatory premotor hyperexcitability, impaired network stability, and dopamine/DBS-sensitive oscillatory markers, underscoring the potential of TMS-EEG as a biomarker for staging, phenotyping, and therapeutic monitoring in PD.

3.3.2. *Progressive supranuclear palsy*

Progressive supranuclear palsy (PSP) is a tauopathy neuropathologically defined by the widespread deposition of hyperphosphorylated tau, accompanied by the formation of tufted astrocytes and globose neurofibrillary tangles across cortical and subcortical structures (Borroni et al., 2014; Boxer et al., 2017). Clinically, PSP is characterized by parkinsonism, vertical supranuclear gaze palsy, and early postural instability with falls, with several phenotypic variants including the classical Richardson syndrome and PSP-parkinsonism (Höglinger et al., 2017). Cognitive impairment, particularly affecting executive and frontal functions, can occur early in the disease course (Boxer et al., 2017; Cosseddu et al., 2017; Pilotto et al., 2017; Steele et al., 1964). The complex symptomatology reflects combined degeneration of cortical and subcortical networks, including the motor cortex, corticospinal tracts, and cortico-cortical connections (Bologna et al., 2017a). Given its ability to directly probe motor cortical circuits, TMS has been extensively applied to investigate PSP pathophysiology over the past three decades (Bologna et al., 2017b; Suppa et al., 2025).

3.3.2.1. *Pathogenic insights from single and paired-pulse TMS.*

Single- and paired-pulse TMS studies have revealed specific alterations in intracortical circuits in PSP. Resting and active motor thresholds are generally preserved, but several studies have reported increased MEP amplitudes at rest and a steeper input–output curve, indicating increased corticospinal excitability (Bologna et al., 2017a; Conte et al., 2012; Fisicaro et al., 2020; Kühn et al., 2004).

A consistent finding across studies is marked SICI reduction, reflecting impaired $GABA_A$-mediated inhibition and motor cortical disinhibition (Benussi et al., 2018b; Bologna et al., 2017a; Conte et al., 2012; Honda et al., 2023; Kühn et al., 2004). This cortical disinhibition is thought to arise either from decreased input to inhibitory interneurons due to degeneration of subcortical or cortico-cortical projections or from direct degeneration of inhibitory interneurons within M1.

Data on $GABA_B$-mediated inhibition are limited. CSP duration was found to be prolonged in two studies (Fisicaro et al., 2020; Kühn et al., 2004), a finding that contrasts with SICI reduction and challenges the simple model of cortical disinhibition, highlighting the need for further investigation. LICI has not been systematically studied in PSP.

Regarding excitatory glutamatergic circuits, most studies reported normal intracortical facilitation (ICF) (Bologna et al., 2017a; Brusa et al., 2014; Conte et al., 2012; Honda et al., 2023; Kühn et al., 2004), although one study showed a reduction in ICF (Benussi et al., 2018b).

The role of cholinergic circuits, as measured by SAI, remains controversial. While some studies found no significant differences compared to healthy controls (Benussi et al., 2018b; Nardone et al., 2005), others reported reduced SAI (Brusa et al., 2014). Importantly, SAI deficits were not restored by two weeks of non-invasive cerebellar stimulation, suggesting that PSP-related cholinergic dysfunction may originate in subcortical regions, such as the nucleus basalis of Meynert, rather than at the cortical level (Nardone et al., 2005).

3.3.2.2. *Cortical plasticity.*

Repetitive TMS protocols have revealed abnormal plasticity mechanisms in PSP. After intermittent theta-burst stimulation (iTBS), MEP amplitude increased to a greater extent in PSP patients compared to controls (Conte et al., 2012; Bologna et al., 2017a). This paradoxical enhancement of plasticity has been correlated with greater disease severity (Conte et al., 2012). The phenomenon is thought to reflect degeneration of inhibitory interneurons within M1, leading to excessive, uncontrolled facilitation of plasticity mechanisms. In contrast, quadripulse stimulation (QPS) revealed a smaller LTP-like effect in PSP compared to healthy controls, and this reduction was negatively correlated with Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) scores, suggesting that impaired plasticity may contribute to greater motor disability (Honda et al., 2023). For a summary of characteristic TMS findings see Table 1.

3.3.2.3. *Cortico-spinal and cortico-cortical connectivity.*

PSP is also associated with alterations in descending and interhemispheric pathways. CMCT is often prolonged, particularly in advanced disease stages, consistent with corticospinal tract involvement (Abbruzzese et al., 1991; Morita et al., 2008). Interhemispheric connectivity, measured using the ipsilateral silent period (iSP), is abnormal in PSP. Reduced transcallosal inhibition has been observed, especially in Richardson syndrome, distinguishing it from PSP-parkinsonism (Wittstock et al., 2012; Wolters et al., 2004). The degree of transcallosal involvement also correlates with cognitive impairment (Wittstock et al., 2012), linking these physiological findings to clinical presentation.

Cerebellar-cortical interactions are consistently impaired, as reflected by reduced CBI. This is measured as the suppressive effect of a conditioning cerebellar pulse on MEPs elicited by contralateral M1 stimulation. The reduction of CBI highlights disruption of the cerebello-thalamo-cortical pathway in PSP (Benussi et al., 2019c; Brusa et al., 2014; Shirota et al., 2010).

No studies have assessed TEPs with TMS-EEG in patients with PSP.

3.3.3. *Corticobasal syndrome*

Corticobasal syndrome (CBS) represents the classical clinical phenotype of corticobasal degeneration, a neurodegenerative tauopathy characterized by the accumulation of hyperphosphorylated tau and astrocytic plaques within cortical and basal ganglia regions (Mahapatra et al., 2004). Clinically, CBS is markedly asymmetric and manifests through a variable combination of parkinsonism, dystonia, and myoclonus, together with higher-order cortical signs such as ideomotor apraxia, alien-limb phenomenon, and cortical sensory loss. Cognitive and behavioural impairments are also frequent, reflecting widespread cortical and subcortical involvement (Armstrong et al., 2013). Importantly, CBS is a clinical syndrome rather than a single pathological entity, as several different underlying neurodegenerative diseases, including corticobasal degeneration, Alzheimer's disease, progressive supranuclear palsy, and frontotemporal lobar degeneration, can give rise to the CBS phenotype. This pathological heterogeneity contributes to variability in clinical presentation and is also expected to influence the neurophysiological findings observed across studies. Despite its clinical relevance, only a limited number of studies have investigated cortical physiology in CBS using TMS.

3.3.3.1. *Pathogenic insights from single and paired-pulse TMS.*

One of the most consistent findings from TMS studies in CBS is the presence of significant alterations in M1 excitability. Several studies have reported reduced MEP amplitudes at rest, likely reflecting direct involvement of corticospinal tract neurons and progressive degeneration of pyramidal output pathways (Kühn et al., 2004; Lu et al., 1998; Valls-Solé et al., 2001). Similarly, a flatter input–output (I/O) curve has been described, which is consistent with impaired corticospinal drive and reduced

recruitment of motor units during voluntary activation (Pal et al., 2008). In addition, motor thresholds tend to be increased or show a trend toward elevation, suggesting global hypoexcitability of the motor cortex (Benussi et al., 2018b; Burrell et al., 2014; Frasson et al., 2003; Kühn et al., 2004; Leiguarda et al., 2003; Pal et al., 2008). These findings indicate a complex interaction between cortical and subcortical pathology, in which both structural and functional components of the corticospinal system are compromised.

Paired-pulse TMS studies have provided important insights into the status of intracortical circuits in CBS. SICI is consistently reduced across studies, indicating marked cortical disinhibition (Alberici et al., 2008; Benussi et al., 2018b; Burrell et al., 2014; Frasson et al., 2003; Hanajima et al., 1996; Kühn et al., 2004; Okuma et al., 2000; Pal et al., 2008). Similarly, CSP duration is shortened, suggesting additional impairment of slower inhibitory mechanisms (Kato, 1997; Kühn et al., 2004; Lu et al., 1998; Pal et al., 2008; Valls-Solé et al., 2001). Together, these findings point to a profound dysfunction of inhibitory interneurons in M1.

The assessment of ICF has yielded more heterogeneous results. While some studies have reported normal ICF values (Alberici et al., 2008; Pal et al., 2008), others have found either increased (Frasson et al., 2003) or decreased facilitation (Benussi et al., 2018b). These discrepancies likely reflect differences in patient populations, disease stage, and methodology. In contrast, cholinergic intracortical circuits, evaluated through SAI, appear to be relatively spared, with no significant alterations detected in CBS (Benussi et al., 2018b). Collectively, these paired-pulse findings suggest a dominant pattern of cortical disinhibition in CBS, primarily due to the loss of GABAergic inhibitory control, accompanied by variable changes in excitatory circuits and relative preservation of cholinergic function.

3.3.3.2. Cortical plasticity. Cortical plasticity in CBS has been less extensively investigated. In the only available study employing intermittent theta-burst stimulation (iTBS), CBS patients showed a lack of MEP amplitude modulation compared to healthy controls, indicating impaired LTP-like plasticity mechanisms within M1. Interestingly, the response to iTBS was not uniform and varied depending on whether the stimulated hemisphere corresponded to the limb manifesting isolated parkinsonism or a combination of parkinsonism and other cortical features such as dystonia or apraxia (Suppa et al., 2016). Another study using low-frequency rTMS reported that cortical inhibition, indexed by the CSP, could be transiently enhanced after stimulation, although no clinical effects were observed, pointing to a potential but limited capacity to modulate cortical excitability in CBS (Civardi et al., 2015).This variability suggests that the degree of plasticity impairment may be closely linked to the clinical topography of CBS and the specific cortical regions affected by the underlying pathology. For a summary of characteristic TMS findings see Table 1.

3.3.3.3. Cortico-cortical connectivity. TMS has also been applied to investigate the integrity of cortico-cortical networks in CBS. Studies using the ipsilateral silent period (iSP) and paired-pulse paradigms have consistently reported reduced transcallosal inhibition from both hemispheres, indicative of disrupted interhemispheric communication and impaired callosal integrity (Pal et al., 2008; Trompetto et al., 2003; Wolters et al., 2004). These changes may contribute to the hallmark asymmetry of CBS as well as to higher-order cortical symptoms. Indeed, reduced transcallosal inhibition has been linked to impairments in verbal fluency and attentional functions (Trompetto et al., 2003). Furthermore, patients presenting with alien limb phenomenon exhibit an expanded cortical representation map in the contralateral hemisphere, consistent with maladaptive cortical reorganization and loss of inhibitory interhemispheric control (Valls-Solé et al., 2001).

3.3.4. Diagnostic utility of TMS in the differential diagnosis of movement disorders

The differential diagnosis of atypical parkinsonian disorders remains a major clinical challenge, particularly in the early stages of disease when clinical features overlap with PD and other neurodegenerative disorders. While imaging and fluid biomarkers have shown promise, their diagnostic performance is mainly limited by lack of specificity in distinguishing among different parkinsonian syndromes.

Two key studies have explored the potential of TMS for classification of movement disorders. In a single-centre study, paired-pulse TMS measures, including SICI, ICF, and SAI, were used to build a decision tree classifier to distinguish between AD, DLB, PSP, CBS, and healthy controls. The classifier achieved an overall diagnostic accuracy of 88.3 %, with accuracies of 90.5 % for AD, 85.2 % for DLB, 76.0 % for CBS/PSP combined, and 94.9 % for healthy controls (Benussi et al., 2018b). Importantly, this approach leveraged the known pathophysiological differences between disorders, such as the predominant cholinergic impairment in AD and DLB versus the GABAergic and glutamatergic interneuron dysfunction characteristic of PSP and CBS, to generate a practical framework for differential diagnosis.

A subsequent study focused specifically on differentiating PSP from other neurodegenerative diseases, including PD, DLB, CBS, FTD, AD, and healthy controls. Using CBI to assess cerebellar-motor connectivity, the authors identified a marked reduction in cerebellar inhibition uniquely associated with PSP. Receiver operating characteristic (ROC) analysis demonstrated excellent diagnostic performance, with an overall area under the curve (AUC) of 0.984, sensitivity of 100 %, specificity of 94.4 %, and accuracy of 95.2 % for distinguishing PSP from all other groups. When directly compared with individual disorders, this paradigm achieved AUC values ranging from 0.93 (PSP vs. FTD) to 1.00 (PSP vs. controls, DLB, and PD). For CBS specifically, the AUC was 0.97 with 100 % sensitivity and 90 % specificity (Benussi et al., 2019c). Notably, similar levels of accuracy were observed even in patients with early PSP, supporting the potential of this measure for early diagnosis.

Collectively, these studies suggest that TMS holds promise for differentiating PSP and CBS from other movement disorders by detecting disease-specific patterns of circuit dysfunction. However, as current evidence comes from single-centre studies, replication in larger, multicentre cohorts is needed before TMS can be integrated into routine clinical practice.

4. Conclusion

Emergent neurophysiological techniques have moved from research tools to clinically meaningful instruments capable of capturing disease-relevant pathophysiology with high temporal resolution and relatively broad accessibility. Across amyotrophic lateral sclerosis, dementias, and movement disorders, the body of evidence presented in this chapter underscores how modalities such as threshold tracking TMS, paired-pulse paradigms, plasticity protocols, and TMS-EEG provide objective biomarkers of cortical excitability, connectivity, and plasticity. Crucially, these measures reveal dysfunction at prodromal or even presymptomatic stages, frequently preceding overt clinical manifestations or structural imaging changes. This temporal advantage is illustrated in Fig. 2, which depicts the sequence of biomarker abnormalities across disease stages, highlighting how alterations in cortical excitability and connectivity may emerge earlier than changes in fluid or imaging markers. This capacity to identify early disease processes aligns with the current paradigm shift in neurology toward presymptomatic and precision-guided interventions.

One of the clearest insights to emerge is that different neurodegenerative syndromes exhibit distinct neurophysiological signatures, often reflecting the preferential involvement of specific neurotransmitter systems. ALS is defined by early cortical hyperexcitability arising from impaired GABAergic interneurons and excess facilitatory drive, detectable through reduction of SICI and elevation of SICF. In AD, consistent

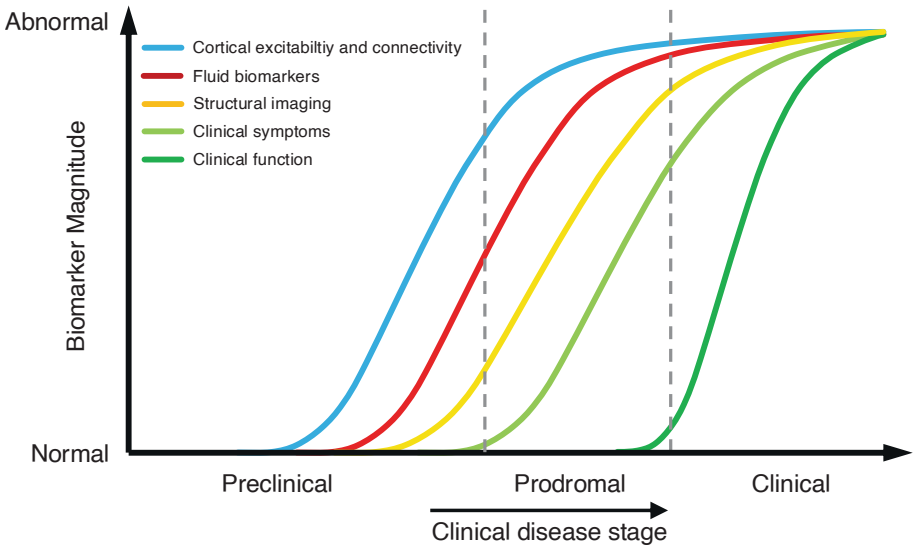

Fig. 2. Temporal evolution of biomarkers across disease stages Conceptual model illustrating how different biomarkers become abnormal over the continuum from preclinical to clinical stages of neurological disease. Alterations in cortical excitability and connectivity detected by TMS and TMS-EEG may occur earliest, preceding abnormalities in fluid biomarkers, structural imaging, and clinical manifestations. This temporal hierarchy highlights the potential of neurophysiological measures for prodromal and presymptomatic detection. Abbreviations: TMS = transcranial magnetic stimulation; TMS-EEG = combined transcranial magnetic stimulation and electroencephalography.

impairment of cholinergic circuits as revealed by reduced SAI, together with aberrant plasticity responses, provides a mechanistic biomarker that parallels disease severity and therapeutic responsiveness. FTD, in contrast, is characterized by combined inhibitory and excitatory dysfunction with sparing of cholinergic transmission, a profile that can be detected even in presymptomatic mutation carriers decades before clinical onset. DLB shows more profound cholinergic involvement than AD and specific alterations in network reactivity that correlate with hallucinations and attentional deficits. In movement disorders, TMS and TMS-EEG highlight progressive gradients of cortical disinhibition across the α-synucleinopathies, and demonstrate unique markers such as reduced CBI in PSP. These pathophysiological profiles not only provide mechanistic insight but also translate into differential diagnostic frameworks with levels of accuracy comparable to established imaging and fluid biomarkers.

The advantages of neurophysiological approaches are manifold. They are non-invasive, relatively inexpensive compared with molecular imaging, and can be applied repeatedly to monitor longitudinal changes or treatment effects. Their temporal resolution allows direct interrogation of excitatory and inhibitory dynamics on the millisecond scale, while their flexibility enables adaptation to probe distinct neurotransmitter systems, networks, or plasticity processes. Importantly, the combination of TMS with EEG provides a unique window into large-scale network reactivity, propagation, and oscillatory dynamics, offering mechanistic insights unattainable with structural or molecular biomarkers. These features also make neurophysiology particularly well suited for integration with novel therapeutic strategies, from pharmacological trials to neuromodulation interventions, where target engagement and circuit-level responses need to be measured directly.

Nonetheless, several limitations must be acknowledged. The implementation of advanced TMS paradigms and TMS-EEG remains largely confined to specialized centres, requiring particular hardware, technical expertise, and standardized protocols. Test-retest variability is a recognized issue for some plasticity measures, underscoring the need for methodological rigor and harmonization across laboratories. Many existing studies have been conducted in single centres with relatively modest sample sizes, raising questions about reproducibility and generalizability. Moreover, while the specificity of neurophysiological signatures for differentiating among diseases has been encouraging, heterogeneity in patient populations, disease stage, and pharmacological state can complicate interpretation. Integration into routine diagnostic workflows will therefore depend on the development of streamlined protocols, automated analysis pipelines, and robust normative datasets.

It should also be acknowledged that alterations in cortical excitability or plasticity, such as reductions in SICI or LTP-like responses, are not disease-specific and can occur across several neurological and psychiatric disorders. These changes likely reflect convergent mechanisms of cortical dysfunction rather than unique diagnostic signatures. Consequently, while these measures are highly sensitive markers of cortical impairment and may be valuable for monitoring disease progression or therapeutic response, their specificity for differential diagnosis remains limited. In individuals with coexisting neurological or systemic conditions, it may not be possible to determine which disorder predominantly contributes to the observed neurophysiological abnormalities.

Another challenge lies in the translational gap between pathophysiological insight and clinical decision-making. While neurophysiological biomarkers can distinguish disease groups with high accuracy, clinicians must balance these findings with clinical examination, imaging, and biochemical assays in real-world practice. Rather than functioning as standalone tests, these techniques are best positioned as complementary tools within a multimodal diagnostic framework. Fig. 3 illustrates this integrative vision of precision neurology, in which TMS and TMS-EEG measures are computationally combined with neuroimaging, fluid biomarkers, and clinical data through advanced analytical models and machine learning, to generate individualized diagnostic and prognostic profiles. Early evidence supports the additive value of such multimodal approaches, which may substantially enhance diagnostic accuracy and translational impact.

Looking forward, several priorities emerge. Large multicentre studies are needed to establish normative values, validate diagnostic performance across settings, and ensure inter-rater reliability. The commercialization and simplification of advanced paradigms, including threshold tracking TMS and real-time TMS-EEG, will broaden accessibility and facilitate adoption in both academic and community settings. Longitudinal studies will clarify the capacity of neurophysiological markers to predict disease onset, monitor progression, and track

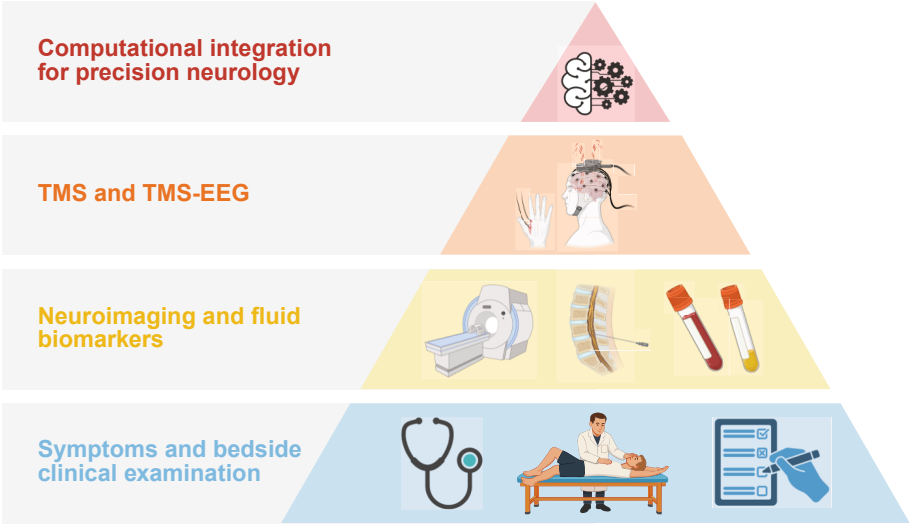

Fig. 3. Computational integration for precision neurology Schematic framework depicting the integration of multimodal information for individualized diagnosis and treatment planning. Neurophysiological data from TMS and TMS-EEG are computationally combined with neuroimaging, fluid biomarkers, and clinical examination to construct predictive models of disease state and trajectory. This "computational integration for precision neurology" approach aims to enable personalized, mechanism-based interventions and real-time monitoring of treatment effects. Abbreviations: EEG = electroencephalography; TMS = transcranial magnetic stimulation; TMS-EEG = combined transcranial magnetic stimulation and electroencephalography.

therapeutic engagement. Finally, combining perturbation-based measures with computational modelling, machine learning, and multimodal biomarkers may yield individualized predictive signatures that transform both clinical trials and everyday practice.

In summary, emergent neurophysiological technologies have reached a tipping point where their clinical potential is no longer speculative but increasingly supported by robust empirical evidence. By directly interrogating the functional state of cortical circuits, they provide mechanistically grounded biomarkers that complement structural, molecular, and clinical assessments. Their integration into diagnostic and therapeutic frameworks promises to improve early detection, enhance differential diagnosis, and guide personalized interventions across a wide spectrum of neurological disorders. While challenges remain, the continued refinement and dissemination of these techniques heralds a new era of precision neurophysiology with substantial implications for the future of neurology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Alberto Benussi has received speaker honoraria from Eli Lilly and Angelini Pharma; he received research grants from Airalzh, Fondazione Cariplo, the Fondation pour la Recherche sur Alzheimer, and the Italian Ministry of University & Research; he is listed as an inventor on issued patents on the use of non-invasive brain stimulation for the differential diagnosis of dementia and to increase cognitive functions in patients with neurodegenerative disorders. Steve Vucic has received speaker honoraria and consultancy fees from Merck Serono Australia, Merck KGaA, Novartis, Bayer Schering, CSL Australia and Biogen Pty Ltd; he has served on scientific advisory boards for Novartis Pharma, Merck Serono Australia and Bayer Schering Australia, and was a medical consultant for Merck Serono Australia until December 2013; he is director of a company that holds equity in Clene Nanomedicine, receives fees from Biogen for advisory board participation, and serves as chair of the Brain Foundation Australia scientific committee; he has received research grants from the Motor Neuron Disease Research Institute of Australia, the Sylvia & Charles Viertel Charitable Foundation, the Ramaciotti Foundation, and the Australian National Health and Medical Research Council].

References

Abbruzzese G, Tabaton M, Morena M, Dall'agata D, Favale E. Motor and Sensory Evoked Potentials in Progressive Supranuclear Palsy. vol. 6. 1991.

Alagona, G., Ferri, R., Pennisi, G., Carnemolla, A., Maci, T., Domina, E., et al., 2004. Motor cortex excitability in Alzheimer's disease and in subcortical ischemic vascular dementia. Neurosci. Lett. 362, 95–98.

Alberici, A., Bonato, C., Calabria, M., Agosti, C., Zanetti, O., Miniussi, C., et al., 2008. The contribution of TMS to frontotemporal dementia variants. Acta Neurol. Scand. 118, 275–280.

Al-Chalabi, A., Calvo, A., Chiò, A., Colville, S., Ellis, C.M., Hardiman, O., et al., 2014. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol. 13, 1108–1113.

Amassian, V.E., Stewart, M., Quirk, G.J., Rosenthal, J.L., 1987. Physiological basis of motor effects of a transient stimulus to cerebral cortex. Neurosurgery 20, 74–93. https://doi.org/10.1097/00006123-198701000-00022.

Ammann, C., Dileone, M., Pagge, C., Catanzaro, V., Mata-Marin, D., Hernandez-Fernandez, F., et al., 2021. Cortical disinhibition in Parkinson's disease. Brain 143, 3408–3421. https://doi.org/10.1093/BRAIN/AWAA274.

Arai, N., Muller-Dahlhaus, F., Murakami, T., Bliem, B., Lu, M.-K., Ugawa, Y., et al., 2011. State-dependent and timing-dependent bidirectional associative plasticity in the human SMA-M1 network. J. Neurosci. 31, 15376–15383. https://doi.org/10.1523/JNEUROSCI.2271-11.2011.

Armstrong, M.J., Litvan, I., Lang, A.E., Bak, T.H., Bhatia, K.P., Borroni, B., et al., 2013. Criteria for the diagnosis of corticobasal degeneration. Neurology 80, 496–503.

Assenza, G., Capone, F., di Biase, L., Ferreri, F., Florio, L., Guerra, A., et al., 2017. Oscillatory activities in neurological disorders of elderly: biomarkers to target for neuromodulation. Front. Aging Neurosci. 9, 1–18. https://doi.org/10.3389/fnagi.2017.00189.

Assogna, M., Casula, E.P., Borghi, I., Bonnì, S., Samà, D., Motta, C., et al., 2020. Effects of palmitoylethanolamide combined with luteoline on frontal lobe functions, high frequency oscillations, and GABAergic transmission in patients with frontotemporal dementia. Journal of Alzheimer's Disease 76, 1297–1308. https://doi.org/10.3233/JAD-200426.

Bae, J.S., Ferguson, M., Tan, R., Mioshi, E., Simon, N., Burrell, J., et al., 2016. Dissociation of structural and functional integrities of the motor system in amyotrophic lateral sclerosis and behavioral-variant frontotemporal dementia. Journal of Clinical Neurology 12, 209–217.

Bae, J.S., Menon, P., Mioshi, E., Kiernan, M.C., Vucic, S., 2014. Cortical hyperexcitability and the split-hand plus phenomenon: pathophysiological insights in ALS. Amyotroph Lateral Scler Frontotemporal Degener 15, 250–256. https://doi.org/10.3109/21678421.2013.872150.

Bagattini, C., Mutanen, T.P., Fracassi, C., Manenti, R., Cotelli, M., Ilmoniemi, R.J., et al., 2019. Predicting Alzheimer's disease severity by means of TMS–EEG coregistration. Neurobiol. Aging 80, 38–45. https://doi.org/10.1016/j.neurobiolaging.2019.04.008.

Bareš, M., Kaňovský, P., Klajblová, H., Rektor, I., 2003. Intracortical inhibition and facilitation are impaired in patients with early Parkinson's disease: a paired TMS study. Eur. J. Neurol. 10, 385–389. https://doi.org/10.1046/j.1468-1331.2003.00610.x.

Bella, R., Cantone, M., Lanza, G., Ferri, R., Vinciguerra, L., Puglisi, V., et al., 2016. Cholinergic circuitry functioning in patients with vascular cognitive impairment – no dementia. Brain Stimul. 9, 225–233.
Benatar, M., Wuu, J., Andersen, P.M., Bucelli, R.C., Andrews, J.A., Otto, M., et al., 2022. Design of a randomized, placebo-controlled, phase 3 trial of tofersen initiated in clinically presymptomatic SOD1 variant carriers: the ATLAS study. Neurotherapeutics 19, 1248–1258. https://doi.org/10.1007/s13311-022-01237-4.
Beniczky, S., Schomer, D.L., 2020. Electroencephalography: basic biophysical and technological aspects important for clinical applications. Epileptic Disord. 22, 697–715. https://doi.org/10.1684/epd.2020.1217.
Benussi, A., Alberici, A., Buratti, E., Ghidoni, R., Gardoni, F., Di Luca, M., et al., 2019a. Toward a glutamate hypothesis of frontotemporal dementia. Front. Neurosci. 13, 304. https://doi.org/10.3389/fnins.2019.00304.
Benussi, A., Alberici, A., Ferrari, C., Cantoni, V., Dell'Era, V., Turrone, R., et al., 2018a. The impact of transcranial magnetic stimulation on diagnostic confidence in patients with Alzheimer disease. Alzheimers Res. Ther. 10, 94. https://doi.org/10.1186/s13195-018-0423-6.
Benussi, A., Ashton, N.J., Karikari, T.K., Gazzina, S., Premi, E., Benussi, L., et al., 2020a. Serum Glial Fibrillary Acidic Protein (GFAP) is a marker of disease severity in frontotemporal lobar degeneration. J. Alzheimers Dis. 77, 1129–1141. https://doi.org/10.3233/JAD-200608.
Benussi, A., Cantoni, V., Borroni, B., 2021. The role of transcranial magnetic stimulation in the diagnosis of dementia, Horizons in Neuroscience Research. Nova Science Publishers Inc, pp. 55–104.
Benussi, A., Cantoni, V., Cotelli, M.S., Cotelli, M., Brattini, C., Datta, A., et al., 2021a. Exposure to gamma tACS in Alzheimer's disease: a randomized, double-blind, sham-controlled, crossover, pilot study. Brain Stimul. 14, 531–540. https://doi.org/10.1016/j.brs.2021.03.007.
Benussi, A., Cantoni, V., Grassi, M., Brechet, L., Michel, C.M., Datta, A., et al., 2022a. Increasing brain gamma activity improves episodic memory and restores cholinergic dysfunction in Alzheimer's disease. Ann. Neurol. 92, 322–334. https://doi.org/10.1002/ana.26411.
Benussi, A., Cantoni, V., Rivolta, J., Archetti, S., Micheli, A., Ashton, N., et al., 2022b. Classification accuracy of blood-based and neurophysiological markers in the differential diagnosis of Alzheimer's disease and frontotemporal lobar degeneration. Alzheimers Res. Ther. 14. https://doi.org/10.1186/s13195-022-01094-5.
Benussi, A., Cosseddu, M., Filareto, I., Dell'Era, V., Archetti, S., Sofia Cotelli, M., et al., 2016. Impaired long-term potentiation-like cortical plasticity in presymptomatic genetic frontotemporal dementia. Ann. Neurol. 80, 472–476. https://doi.org/10.1002/ana.24731.
Benussi, A., Dell'Era, V., Cantoni, V., Cotelli, M.S., Cosseddu, M., Spallazzi, M., et al., 2020b. Neurophysiological correlates of positive and negative symptoms in frontotemporal dementia. J. Alzheimers Dis. 73, 1133–1142. https://doi.org/10.3233/JAD-190986.
Benussi, A., Dell'Era, V., Cantoni, V., Cotelli, M.S., Cosseddu, M., Spallazzi, M., et al., 2020c. TMS for staging and predicting functional decline in frontotemporal dementia. Brain Stimul. 13, 386–392. https://doi.org/10.1016/j.brs.2019.11.009.
Benussi, A., Dell'Era, V., Cantoni, V., Ferrari, C., Caratozzolo, S., Rozzini, L., et al., 2018b. Discrimination of atypical parkinsonisms with transcranial magnetic stimulation. Brain Stimul. 11, 366–373. https://doi.org/10.1016/j.brs.2017.11.013.
Benussi A, Dell'Era V, Cantoni V, Padovani A, Borroni B. The impact of TMS on the differential diagnosis and progression of dementia. Brain Stimul, vol. 12, Elsevier Ltd; 2019b, p. 504. 10.1016/j.brs.2018.12.652.
Benussi, A., Dell'Era, V., Cantoni, V., Turrone, R., Pilotto, A., Alberici, A., et al., 2019c. Stimulation over the cerebellum with a regular figure-of-eight coil induces reduced motor cortex inhibition in patients with progressive supranuclear palsy. Brain Stimul. 12, 1290–1297. https://doi.org/10.1016/j.brs.2019.05.017.
Benussi, A., Dell'era, V., Cosseddu, M., Cantoni, V., Cotelli, M.S., Cotelli, M., et al., 2020d. Transcranial stimulation in frontotemporal dementia: a randomized, double-blind, sham-controlled trial. Alzheimer's and Dementia: Translational Research and Clinical Interventions 6, 1–11. https://doi.org/10.1002/trc2.12033.
Benussi, A., Gazzina, S., Premi, E., Cosseddu, M., Archetti, S., Dell'Era, V., et al., 2019d. Clinical and biomarker changes in presymptomatic genetic frontotemporal dementia. Neurobiol. Aging 76, 133–140. https://doi.org/10.1016/j.neurobiolaging.2018.12.018.
Benussi, A., Grassi, M., Palluzzi, F., Cantoni, V., Cotelli, M.S., Premi, E., et al., 2021b. Classification accuracy of TMS for the diagnosis of mild cognitive impairment. Brain Stimul. 14, 241–249. https://doi.org/10.1016/j.brs.2021.01.004.
Benussi, A., Grassi, M., Palluzzi, F., Koch, G., Di Lazzaro, V., Nardone, R., et al., 2020e. Classification accuracy of transcranial magnetic stimulation for the diagnosis of neurodegenerative dementias. Ann. Neurol. 87, 394–404. https://doi.org/10.1002/ana.25677.
Benussi, A., Huber, H., Tan, K., Cantoni, V., Rivolta, J., Cotelli, M.S., et al., 2025. Plasma p-tau217 and neurofilament/p-tau217 ratio in differentiating Alzheimer's disease from syndromes associated with frontotemporal lobar degeneration. Alzheimer's and Dementia. https://doi.org/10.1002/alz.14482.
Benussi, A., Karikari, T.K., Ashton, N., Gazzina, S., Premi, E., Benussi, L., et al., 2020f. Diagnostic and prognostic value of serum NfL and p-Tau 181 in frontotemporal lobar degeneration. J. Neurol. Neurosurg. Psychiatry 91, 960–967. https://doi.org/10.1136/jnnp-2020-323487.
Benussi, A., Di Lorenzo, F., Dell'Era, V., Cosseddu, M., Alberici, A., Caratozzolo, S., et al., 2017a. Sensitivity and specificity of transcranial magnetic stimulation for differential diagnosis of Alzheimer's disease and frontotemporal dementia. Alzheimer's & Dementia P695–P696.
Benussi, A., Di Lorenzo, F., Dell'Era, V., Cosseddu, M., Alberici, A., Caratozzolo, S., et al., 2017b. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. Neurology 89, 665–672. https://doi.org/10.1212/WNL.0000000000004232.
Benussi, A., Padovani, A., Borroni, B., 2015. Phenotypic heterogeneity of monogenic frontotemporal dementia. Front. Aging Neurosci. 7, 171. https://doi.org/10.3389/fnagi.2015.00171.
Benussi, A., Pilotto, A., Cantoni, V., Ferrari, E., Borroni, B., Padovani, A., 2022c. Neurophysiological correlates of motor and cognitive dysfunction in prodromal and overt dementia with lewy bodies. Journal of Alzheimer's Disease 86, 579–588. https://doi.org/10.3233/JAD-215531.
Benussi, A., Premi, E., Gazzina, S., Cantoni, V., Cotelli, M.S., Giunta, M., et al., 2020g. Neurotransmitter imbalance dysregulates brain dynamic fluidity in frontotemporal degeneration. Neurobiol. Aging 94, 176–184. https://doi.org/10.1016/j.neurobiolaging.2020.05.017.
Berardelli, A., Rona, S., Inghilleri, M., Manfredi, M., 1996. Cortical inhibition in Parkinson's disease. a study with paired magnetic stimulation. Brain 119 (Pt 1), 71–77. https://doi.org/10.1093/brain/119.1.71.
Berlanga, M.L., Simpson, T.K., Alcantara, A.A., 2005. Dopamine D5 receptor localization on cholinergic neurons of the rat forebrain and diencephalon: a potential neuroanatomical substrate involved in mediating dopaminergic influences on acetylcholine release. J Comp Neurol 492, 34–49. https://doi.org/10.1002/cne.20684.
Bernardi, D., Casula, E.P., Rocchi, L., Fadiga, L., Koch, G., Papo, D., 2025. Multivariate empirical mode decomposition reveals markers of Alzheimer's Disease in the oscillatory response to transcranial magnetic stimulation. Clin. Neurophysiol. 176. https://doi.org/10.1016/j.clinph.2025.2110756.
Blair, I.P., Williams, K.L., Warraich, S.T., Durnall, J.C., Thoeng, A.D., Manavis, J., et al., 2010. FUS mutations in amyotrophic lateral sclerosis: clinical, pathological, neurophysiological and genetic analysis. J. Neurol. Neurosurg. Psychiatry 81, 639–645.
Bloem, B.R., Okun, M.S., Klein, C., 2021. Parkinson's disease. Lancet 397, 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X.
Boillée, S., Vande Velde, C., Cleveland, D.W.W., 2006. ALS: a disease of motor neurons and their nonneuronal neighbors. Neuron 52, 39–59. https://doi.org/10.1016/j.neuron.2006.09.018.
Bologna, M., Bertram, K., Paparella, G., Papi, C., Belvisi, D., Conte, A., et al., 2017a. Reversal of long term potentiation-like plasticity in primary motor cortex in patients with progressive supranuclear palsy. Clin. Neurophysiol. 128, 1547–1552. https://doi.org/10.1016/j.clinph.2017.06.032.
Bologna, M., Guerra, A., Paparella, G., Giordo, L., Fegatelli, D.A., Vestri, A.R., et al., 2018. Neurophysiological correlates of bradykinesia in Parkinson's disease. Brain 141, 2432–2444. https://doi.org/10.1093/brain/awy155.
Bologna, M., Suppa, A., Di Stasio, F., Conte, A., Fabbrini, G., Berardelli, A., 2017b. Neurophysiological studies on atypical parkinsonian syndromes. Parkinsonism Relat. Disord. 42, 12–21. https://doi.org/10.1016/j.parkreldis.2017.06.017.
Bonanni, L., Perfetti, B., Bifolchetti, S., Taylor, J.P., Franciotti, R., Parnetti, L., et al., 2015. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol. Aging 36, 434–445. https://doi.org/10.1016/j.neurobiolaging.2014.07.009.
Bonnì, S., Lupo, F., Lo Gerfo, E., Martorana, A., Perri, R., Caltagirone, C., et al., 2013. Altered parietal-motor connections in Alzheimer's disease patients. J. Alzheimers Dis. 33, 525–533.
Borroni B, Benussi A. Recent advances in understanding frontotemporal degeneration. F1000Res 2019;8:2098. 10.12688/f1000research.20330.1.
Borroni, B., Benussi, A., Pilotto, A., Gazzina, S., Turrone, R., Gardoni, F., et al., 2014. Diagnosing progressive supranuclear palsy: role of biological and neuroimaging markers. J Alzheimers Dis Parkinsonism 04, 10.4172/2161-0460.1000168.
Borroni, B., Benussi, A., Premi, E., Alberici, A., Marcello, E., Gardoni, F., et al., 2018. Biological, neuroimaging, and neurophysiological markers in frontotemporal dementia: three faces of the same coin. J. Alzheimers Dis. 62, 1113–1123. https://doi.org/10.3233/JAD-170584.
Van Den Bos, M.A.J., Higashihara, M., Geevasinga, N., Menon, P., Kiernan, M.C., Vucic, S., 2018. Imbalance of cortical facilitatory and inhibitory circuits underlies hyperexcitability in ALS. Neurology 91, E1669–E1676. https://doi.org/10.1212/WNL.0000000000006438.
Van den Bos, M.A.J., Menon, P., Howells, J., Geevasinga, N., Kiernan, M.C., Vucic, S., 2018. Physiological processes underlying short interval intracortical facilitation in the human motor cortex. Front. Neurosci. 12, 74.
van den Bos, M.A.J., Menon, P., Pavey, N., Higashihara, M., Kiernan, M.C., Vucic, S., 2025. Direct interrogation of cortical interneuron circuits in amyotrophic lateral sclerosis. Brain 148, 1169–1179. https://doi.org/10.1093/brain/awae317.
Boxer, A.L., Yu, J.-T., Golbe, L.I., Litvan, I., Lang, A.E., Höglinger, G.U., 2017. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurol. 16, 552–563.
Bracca, V., Cantoni, V., Gadola, Y., Rivolta, J., Cosseddu, M., Turrone, R., et al., 2023. Neurophysiological correlates of altered time awareness in Alzheimer's disease and frontotemporal dementia. Neurol. Sci. https://doi.org/10.1007/s10072-023-06877-8.
Brem, A.-K., Atkinson, N.J., Seligson, E.E., Pascual-Leone, A., 2013. Differential pharmacological effects on brain reactivity and plasticity in Alzheimer's disease. Front. Psych. 4, 124.
Brier, M., Thomas, J.B., Snyder, A.Z., Benzinger, T.L., Zhang, D., 2012. Loss of Intra- and Inter-network resting state functional connections with Alzheimer's disease progression. J. Neurosci. 32, 8890–8899. https://doi.org/10.1523/JNEUROSCI.5698-11.2012.Loss.
Brooks, B.R., 1994. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/

Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J. Neurol. Sci. 124, 96–107.
Brooks, B.R., Miller, R.G., Swash, M., Munsat, T.L., 2000. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1, 293–299.
Brusa, L., Ponzo, V., Mastropasqua, C., Picazio, S., Bonnì, S., Di Lorenzo, F., et al., 2014. Theta burst stimulation modulates cerebellar-cortical connectivity in patients with progressive supranuclear palsy. Brain Stimul. 7, 29–35.
Buch, E.R., Mars, R.B., Boorman, E.D., Rushworth, M.F.S., 2010. A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J. Neurosci. 30, 1395–1401. https://doi.org/10.1523/jneurosci.4882-09.2010.
Burrell, J.R., Hornberger, M., Vucic, S., Kiernan, M.C., Hodges, J.R., 2014. Apraxia and motor dysfunction in corticobasal syndrome. PLoS One 9, e92944.
Burrell, J.R., Kiernan, M.C., Vucic, S., Hodges, J.R., 2011. Motor Neuron dysfunction in frontotemporal dementia. Brain 134, 2582–2594. https://doi.org/10.1093/brain/awr195.
Calma, A.D., Pavey, N., Silva, C.S., van den Bos, M.A.J., Yiannikas, C., Farrar, M.A., et al., 2025. Diagnostic utility of threshold tracking TMS paradigms in early amyotrophic lateral sclerosis. Clin. Neurophysiol. 174, 105–113. https://doi.org/10.1016/j.clinph.2025.03.044.
Canali, P., Casarotto, S., Rosanova, M., Sferrazza-Papa, G., Casali, A.G., Gosseries, O., et al., 2017. Abnormal brain oscillations persist after recovery from bipolar depression. Eur. Psychiatry 41, 10–15. https://doi.org/10.1016/j.eurpsy.2016.10.005.
Cantello, R., 2002. Applications of transcranial magnetic stimulation in movement disorders. J. Clin. Neurophysiol. 19, 272–293.
Cantello, R., Gianelli, M., Bettucci, D., Civardi, C., De Angelis, M.S., Mutani, R., 1991. Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. Neurology 41, 1449–1456. https://doi.org/10.1212/wnl.41.9.1449.
Cantello, R., Gianelli, M., Civardi, C., Mutani, R., 1992. Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42, 1951–1959.
Carrillo, F., Palomar, F.J., Conde, V., Diaz-Corrales, F.J., Porcacchia, P., Fernández-del-Olmo, M., et al., 2013. Study of cerebello-thalamocortical pathway by transcranial magnetic stimulation in Parkinson's disease. Brain Stimul. 6, 582–589.
de Carvalho, M., Dengler, R., Eisen, A., England, J.D., Kaji, R., Kimura, J., et al., 2008. Electrodiagnostic criteria for diagnosis of ALS. Clin. Neurophysiol. 119, 497–503.
de Carvalho, M., 1997. de Mendon x000E7 a a, Miranda PC, Garcia C, s MLSL x000ED. magnetic stimulation in Alzheimer's disease. J. Neurol. 244, 304–307.
Casarotto, S., Määttä, S., Herukka, S.K., Pigorini, A., Napolitani, M., Gosseries, O., et al., 2011. Transcranial magnetic stimulation-evoked EEG/cortical potentials in physiological and pathological aging. Neuroreport 22, 592–597. https://doi.org/10.1097/WNR.0b013e328349433a.
Casarotto, S., Turco, F., Comanducci, A., Perretti, A., Marotta, G., Pezzoli, G., et al., 2019. Excitability of the supplementary motor area in Parkinson's disease depends on subcortical damage. Brain Stimul. 12, 152–160. https://doi.org/10.1016/j.brs.2018.10.011.
Casula, E.P., Borghi, I., Maiella, M., Pellicciari, M.C., Bonnì, S., Mencarelli, L., et al., 2023. Regional precuneus cortical hyperexcitability in Alzheimer's disease patients. Ann. Neurol. 93, 371–383. https://doi.org/10.1002/ana.26514.
Casula, E.P., Pellicciari, M.C., Bonnì, S., Borghi, I., Maiella, M., Assogna, M., et al., 2022. Decreased frontal gamma activity in Alzheimer disease patients. Ann. Neurol. 92, 464–475. https://doi.org/10.1002/ana.26444.
Casula, E.P., Stampanoni Bassi, M., Pellicciari, M.C., Ponzo, V., Veniero, D., Peppe, A., et al., 2017. Subthalamic stimulation and levodopa modulate cortical reactivity in Parkinson's patients. Parkinsonism Relat. Disord. 34, 31–37. https://doi.org/10.1016/j.parkreldis.2016.10.009.
Celebi, O., Temuçin, C.M., Elibol, B., Saka, E., 2012. Short latency afferent inhibition in Parkinson's disease patients with dementia. Mov. Disord. 27, 1052–1055.
Chandra, S.R., Issac, T.G., Nagaraju, B.C., Philip, M., 2016. A study of cortical excitability, central motor conduction, and cortical inhibition using single pulse transcranial magnetic stimulation in patients with early frontotemporal and Alzheimer's dementia. Indian J. Psychol. Med. 38, 25–30.
Chao, C.C., Karabanov, A.N., Paine, R., Carolina De Campos, A., Kukke, S.N., Wu, T., et al., 2015. Induction of motor associative plasticity in the posterior parietal cortex-primary motor network. Cereb. Cortex 25, 365–373. https://doi.org/10.1093/cercor/bht230.
Chen, R., 2004. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp. Brain Res. 154, 1–10.
Chen, R., Cros, D., Curra, A., Di Lazzaro, V., Lefaucheur, J.P., Magistris, M.R., et al., 2008. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin. Neurophysiol. 119, 504–532.
Chen, R., Lozano, A.M., Ashby, P., 1999. Mechanism of the silent period following transcranial magnetic stimulation. evidence from epidural recordings. Exp. Brain Res. 128, 539–542. https://doi.org/10.1007/s002210050878.
Chen R, Rothwell JC, editors. Cortical Connectivity. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. 10.1007/978-3-642-32767-4.
Chu, J., Wagle-Shukla, A., Gunraj, C., Lang, A.E., Chen, R., 2009. Impaired presynaptic inhibition in the motor cortex in Parkinson disease. Neurology 72, 842–849.
Civardi, C., Pisano, F., Delconte, C., Collini, A., Monaco, F., 2015. Effects of slow repetitive transcranial magnetic stimulation in patients with corticobasal syndrome. Neurol. Sci. 36, 1007–1009. https://doi.org/10.1007/S10072-015-2115-3/FIGURES/1.
Clark, C.M., Clark, R.M., Hoyle, J.A., Chuckowree, J.A., McLean, C.A., Dickson, T.C., 2021. Differential NPY-Y1 receptor density in the motor cortex of ALS patients and familial model of ALS. Brain Sci. 11, 969. https://doi.org/10.3390/brainsci11080969.
Claus, D., Weis, M., Jahnke, U., Plewe, A., Brunhölzl, C., 1992. Corticospinal conduction studied with magnetic double stimulation in the intact human. J. Neurol. Sci. 111, 180–188. https://doi.org/10.1016/0022-510X(92)90066-T.
Conte, A., Belvisi, D., Bologna, M., Ottaviani, D., Fabbrini, G., Colosimo, C., et al., 2012. Abnormal cortical synaptic plasticity in primary motor area in progressive supranuclear palsy. Cereb. Cortex 22, 693–700.
Cosseddu, M., Benussi, A., Gazzina, S., Manes, M.A., Dell'Era, V., Cristillo, V., et al., 2017. Natural history and predictors of survival in progressive supranuclear palsy. J. Neurol. Sci. 382, 105–107. https://doi.org/10.1016/j.jns.2017.09.043.
Costa, J., Swash, M., de Carvalho, M., 2012. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis:a systematic review. Arch. Neurol. 69, 1410–1416. https://doi.org/10.1001/archneurol.2012.254.
Cunic, D., Roshan, L., Khan, F.I., Lozano, A.M., Lang, A.E., Chen, R., 2002. Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. Neurology 58, 1665–1672. https://doi.org/10.1212/wnl.58.11.1665.
Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B., Roshan, L., Chen, R., 2002. The mechanisms of interhemispheric inhibition in the human motor cortex. J. Physiol. 543, 317–326. https://doi.org/10.1113/jphysiol.2002.017673.
Davila-Pérez, P., Jannati, A., Fried, P.J., Cudeiro Mazaira, J., Pascual-Leone, A., 2018. The effects of waveform and current direction on the efficacy and test–retest reliability of transcranial magnetic stimulation. Neuroscience 393, 97–109. https://doi.org/10.1016/j.neuroscience.2018.09.044.
Dennis, E.L., Thompson, P.M., 2014. Functional brain connectivity using fMRI in aging and Alzheimer's disease. Neuropsychol. Rev. 24, 49–62.
Devine, M.S., Kiernan, M.C., Heggie, S., McCombe, P.A., Henderson, R.D., 2014. Study of motor asymmetry in ALS indicates an effect of limb dominance on onset and spread of weakness, and an important role for upper motor neurons. Amyotroph Lateral Scler Frontotemporal Degener 15, 481–487. https://doi.org/10.3109/21678421.2014.906617.
Dharmadasa, T., Henderson, R.D., Talman, P.S., Al Macdonell, R., Mathers, S., Schultz, D. W., et al., 2017. Motor neurone disease: progress and challenges. Med. J. Aust. 206, 357–362. https://doi.org/10.5694/MJA16.01063.
Dharmadasa, T., Matamala, J.M., Howells, J., Vucic, S., Kiernan, M.C., 2020. Early focality and spread of cortical dysfunction in amyotrophic lateral sclerosis: a regional study across the motor cortices. Clin. Neurophysiol. 131, 958–966. https://doi.org/10.1016/j.clinph.2019.11.057.
Dharmadasa, T., Pavey, N., Tu, S., Menon, P., Huynh, W., Mahoney, C.J., et al., 2024. Novel approaches to assessing upper motor neuron dysfunction in motor neuron disease/amyotrophic lateral sclerosis: IFCN handbook chapter. Clin. Neurophysiol. 163, 68–89. https://doi.org/10.1016/j.clinph.2024.04.010.
Dubbioso, R., Madsen, K.H., Thielscher, A., Siebner, H.R., 2021. The myelin content of the human precentral hand knob reflects interindividual differences in manual motor control at the physiological and behavioral level. J. Neurosci. 41, 3163–3179. https://doi.org/10.1523/JNEUROSCI.0390-20.2021.
Dubbioso, R., Manganelli, F., Siebner, H.R., Di Lazzaro, V., 2019. Fast intracortical sensory-motor integration: a window into the pathophysiology of Parkinson's disease. Front. Hum. Neurosci. 13, 111. https://doi.org/10.3389/fnhum.2019.00111.
Dubbioso, R., Raffin, E., Karabanov, A., Thielscher, A., Siebner, H.R., 2017. Centre-surround organization of fast sensorimotor integration in human motor hand area. Neuroimage 158, 37–47. https://doi.org/10.1016/j.neuroimage.2017.06.063.
van Dyck, C.H., Swanson, C.J., Aisen, P., Bateman, R.J., Chen, C., Gee, M., et al., 2023. Lecanemab in early Alzheimer's disease. N. Engl. J. Med. 388, 9–21. https://doi.org/10.1056/NEJMoa2212948.
Eisen, A., Braak, H., Del Tredici, K., Lemon, R., Ludolph, A.C., Kiernan, M.C., 2017. Cortical influences drive amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 88, 917–924.
Eisen, A., Kim, S., Pant, B., 1992. Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotoneuron? Muscle Nerve 15, 219–224. https://doi.org/10.1002/mus.880150215.
Ellaway PH, Davey NJ, Maskill DW, Dick JPR. The relation between bradykinesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects. vol. 97. 1995.
Engelborghs, S., Niemantsverdriet, E., Struyfs, H., Blennow, K., Brouns, R., Comabella, M., et al., 2017. Consensus guidelines for lumbar puncture in patients with neurological diseases Alzheimer's & dementia: diagnosis. Assessment & Disease Monitoring 8, 111–126.
Esmaeeli, S., Murphy, K., Swords, G.M., Ibrahim, B.A., Brown, J.W., Llano, D.A., 2019. Visual hallucinations, thalamocortical physiology and Lewy body disease: a review. Neurosci. Biobehav. Rev. 103, 337–351. https://doi.org/10.1016/j.neubiorev.2019.06.006.
Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., Marsden, C.D., 1992. Interhemispheric inhibition of the human motor cortex. J. Physiol. 453, 525–546. https://doi.org/10.1113/jphysiol.1992.sp019243.
Ferreri, F., Guerra, A., Vollero, L., Ponzo, D., Määttä, S., Könönen, M., et al., 2021. TMS-EEG biomarkers of amnestic mild cognitive impairment due to Alzheimer's disease: a proof-of-concept six years prospective study. Front. Aging Neurosci. 13. https://doi.org/10.3389/fnagi.2021.737281.
Ferreri, F., Pasqualetti, P., Määttä, S., Ponzo, D., Guerra, A., Bressi, F., et al., 2011. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation follow-up study. Neurosci. Lett. 492, 94–98.
Ferreri, F., Pauri, F., Pasqualetti, P., Fini, R., Dal Forno, G., Rossini, P.M., 2003. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation study. Ann. Neurol. 53, 102–108.

Ferreri, F., Vecchio, F., Vollero, L., Guerra, A., Petrichella, S., Ponzo, D., et al., 2016. Sensorimotor cortex excitability and connectivity in Alzheimer's disease: a TMS-EEG Co-registration study. Hum. Brain Mapp. 37, 2083–2096.
Ferullo, L., Risi, B., Caria, F., Olivieri, E., Poli, L., Gazzina, S., et al., 2024. Gold coast criteria in ALS diagnosis: a real-world experience. Brain Sci. 14. https://doi.org/10.3390/brainsci14111055.
Fischer, L.R., Culver, D.G., Tennant, P., Davis, A.A., Wang, M., Castellano-Sanchez, A., et al., 2004. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. Exp. Neurol. 185, 232–240.
Fisher, R.J., Nakamura, Y., Bestmann, S., Rothwell, J.C., Bostock, H., 2002. Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. Exp. Brain Res. 143, 240–248.
Fisicaro, F., Lanza, G., Cantone, M., Ferri, R., Pennisi, G., Nicoletti, A., et al., 2020. Clinical and electrophysiological hints to tms in de novo patients with parkinson's disease and progressive supranuclear palsy. J Pers Med 10, 1–16. https://doi.org/10.3390/jpm10040274.
Foerster, B.R., Callaghan, B.C., Petrou, M., Edden, R.A., Chenevert, T.L., Feldman, E.L., 2012. Decreased motor cortex gamma-aminobutyric acid in amyotrophic lateral sclerosis. Neurology 78, 1596–1600. https://doi.org/10.1212/WNL.0b013e3182563b57.
Fontana, E., Bongianni, M., Benussi, A., Bronzato, E., Scialo, C., Sacchetto, L., et al., 2023. Detection of TDP-43 seeding activity in the olfactory mucosa from patients with frontotemporal dementia. Alzheimer's and Dementia. https://doi.org/10.1002/alz.13541.
Frasson, E., Bertolasi, L., Bertasi, V., Fusina, S., Bartolomei, L., Vicentini, S., et al., 2003. Paired transcranial magnetic stimulation for the early diagnosis of corticobasal degeneration. Clin. Neurophysiol. 114, 272–278.
Freitas, C., Perez, J., Knobel, M., Tormos, J.M., Oberman, L., Eldaief, M., et al., 2011. Changes in cortical plasticity across the lifespan. Front. Aging Neurosci. 3, 5.
Fried, P.J., Schilberg, L., Brem, A.K., Saxena, S., Wong, B., Cypess, A.M., et al., 2016. Humans with type-2 diabetes show abnormal long-term potentiation-like cortical plasticity associated with verbal learning deficits. Journal of Alzheimer's Disease 55, 89–100. https://doi.org/10.3233/JAD-160505.
Frisoni, G.B., Boccardi, M., Barkhof, F., Blennow, K., Cappa, S., Chiotis, K., et al., 2017. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol. 16, 661–676. https://doi.org/10.1016/S1474-4422(17)30159-X.
Gargiulo-Monachelli, G.M., Janota, F., Bettini, M., Shoesmith, C.L., Strong, M.J., Sica, R. E., 2012. Regional spread pattern predicts survival in patients with sporadic amyotrophic lateral sclerosis. Eur. J. Neurol. 19, 834–841. https://doi.org/10.1111/j.1468-1331.2011.03616.x.
Gazzina, S., Benussi, A., Premi, E., Paternicò, D., Cristillo, V., Dell'Era, V., et al., 2018. Neuroanatomical correlates of transcranial magnetic stimulation in presymptomatic granulin mutation carriers. Brain Topogr. 31, 488–497. https://doi.org/10.1007/s10548-017-0612-9.
Geevasinga, N., Loy, C.T., Menon, P., de Carvalho, M., Swash, M., Schrooten, M., et al., 2016a. Awaji criteria improves the diagnostic sensitivity in amyotrophic lateral sclerosis: a systematic review using individual patient data. Clin. Neurophysiol. 127, 2684–2691. https://doi.org/10.1016/j.clinph.2016.04.005.
Geevasinga, N., Menon, P., Ng, K., Van Den Bos, M., Byth, K., Kiernan, M.C., et al., 2016b. Riluzole exerts transient modulating effects on cortical and axonal hyperexcitability in ALS. Amyotroph Lateral Scler Frontotemporal Degener 17, 580–588.
Geevasinga, N., Menon, P., Özdinler, P.H., Kiernan, M.C., Vucic, S., 2016c. Pathophysiological and diagnostic implications of cortical dysfunction in ALS. Nat. Rev. Neurol. 12, 651–661.
Geevasinga, N., Menon, P., Sue, C.M., Kumar, K.R., Ng, K., Yiannikas, C., et al., 2015. Cortical excitability changes distinguish the motor neuron disease phenotypes from hereditary spastic paraplegia. Eur. J. Neurol. 22 (826–31), e57–e58. https://doi.org/10.1111/ene.12669.
Geevasinga, N., Menon, P., Yiannikas, C., Kiernan, M.C., Vucic, S., 2014. Diagnostic utility of cortical excitability studies in amyotrophic lateral sclerosis. Eur. J. Neurol. 21, 1451–1457.
Gilio, F., Currà, A., Inghilleri, M., Lorenzano, C., Manfredi, M., Berardelli, A., 2002. Repetitive magnetic stimulation of cortical motor areas in Parkinson's disease: implications for the pathophysiology of cortical function. Mov Disord 17, 467–473.
Giovannelli, F., Borgheresi, A., Balestrieri, F., Zaccara, G., Viggiano, M.P., Cincotta, M., et al., 2009. Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. J. Physiol. 587, 5393–5410. https://doi.org/10.1113/jphysiol.2009.175885.
Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., et al., 2011. Classification of primary progressive aphasia and its variants. Neurology 76, 1006–1014.
Gross, J., 2019. Magnetoencephalography in cognitive neuroscience: a primer. Neuron 104, 189–204. https://doi.org/10.1016/j.neuron.2019.07.001.
Grossman, M., Seeley, W.W., Boxer, A.L., Hillis, A.E., Knopman, D.S., Ljubenov, P.A., et al., 2023. Frontotemporal lobar degeneration. Nat. Rev. Dis. Primers 9. https://doi.org/10.1038/s41572-023-00447-0.
Guerra, A., Suppa, A., D'Onofrio, V., Di Stasio, F., Asci, F., Fabbrini, G., et al., 2019. Abnormal cortical facilitation and L-dopa-induced dyskinesia in Parkinson's disease. Brain Stimul. 12, 1517–1525. https://doi.org/10.1016/j.brs.2019.06.012.
Haidar, M., Viden, A., Daniel, C., Cuic, B., Wang, T., Rosier, M., et al., 2025. Cortical hyperexcitability drives dying forward amyotrophic lateral sclerosis symptoms and pathology in mice. Prog. Neurobiol. 252, 102809. https://doi.org/10.1016/j.pneurobio.2025.102809.
Hallett, M., 2007. Transcranial magnetic stimulation: a primer. Neuron 55, 187–199.
Hampel, H., Gao, P., Cummings, J., Toschi, N., Thompson, P.M., Hu, Y., et al., 2023. The foundation and architecture of precision medicine in neurology and psychiatry. Trends Neurosci. 46, 176–198. https://doi.org/10.1016/j.tins.2022.12.004.
Han, J.Y., Jang, H.S., Green, A.J.E., Choi, Y.P., 2020. RT-QuIC-based detection of alpha-synuclein seeding activity in brains of dementia with Lewy Body patients and of a transgenic mouse model of synucleinopathy. Prion 14, 88–94. https://doi.org/10.1080/19336896.2020.1724608.
Hanajima, R., Furubayashi, T., Iwata, N.K., Shiio, Y., Okabe, S., Kanazawa, I., et al., 2003. Further evidence to support different mechanisms underlying intracortical inhibition of the motor cortex. Exp. Brain Res. 151, 427–434.
Hanajima, R., Terao, Y., Shirota, Y., Ohminami, S., Nakatani-Enomoto, S., Okabe, S., et al., 2011. Short-interval intracortical inhibition in Parkinson's disease using anterior-posterior directed currents. Exp. Brain Res. 214, 317–321. https://doi.org/10.1007/s00221-011-2829-2.
Hanajima, R., Ugawa, Y., Terao, Y., Enomoto, H., Shiio, Y., Mochizuki, H., et al., 2002. Mechanisms of intracortical I-wave facilitation elicited with paired-pulse magnetic stimulation in humans. J. Physiol. 538, 253–261.
Hanajima, R., Ugawa, Y., Terao, Y., Ogata, K., Kanazawa, I., 1996. Ipsilateral cortico-cortical inhibition of the motor cortex in various neurological disorders. J. Neurol. Sci. 140, 109–116. https://doi.org/10.1016/0022-510X(96)00100-1.
Hanajima, R., Ugawa, Y., Terao, Y., Sakai, K., Furubayashi, T., Machii, K., et al., 1998. Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J. Physiol. 509, 607–618.
Hannaford, A., Pavey, N., van den Bos, M., Geevasinga, N., Menon, P., Shefner, J.M., et al., 2021. Diagnostic utility of gold coast criteria in amyotrophic lateral sclerosis. Ann. Neurol. 89, 979–986. https://doi.org/10.1002/ana.26045.
Hernandez-Pavon, J.C., Veniero, D., Bergmann, T.O., Belardinelli, P., Bortoletto, M., Casarotto, S., et al., 2023. TMS combined with EEG: recommendations and open issues for data collection and analysis. Brain Stimul. 16, 567–593. https://doi.org/10.1016/j.brs.2023.02.009.
Hoeppner, J., Wegrzyn, M., Thome, J., Bauer, A., Oltmann, I., Buchmann, J., et al., 2012. Intra- and inter-cortical motor excitability in Alzheimer's disease. J. Neural Transm. 119, 605–612.
Höglinger, G.U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K.A., Lang, A.E., et al., 2017. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov. Disord. 32, 853–864. https://doi.org/10.1002/mds.26987.
Honda, M., Shimizu, T., Moriyasu, S., Murakami, T., Takigawa, H., Ugawa, Y., et al., 2023. Impaired long-term potentiation-like motor cortical plasticity in progressive supranuclear palsy. Clin. Neurophysiol. 155, 99–106. https://doi.org/10.1016/j.clinph.2023.07.011.
Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45, 201–206.
Huang, Y.-Z., Lu, M.-K., Antal, A., Classen, J., Nitsche, M.A., Ziemann, U., et al., 2017. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. Clin. Neurophysiol. 128, 2318–2329.
Hwang, Y.T., Rocchi, L., Hammond, P., Hardy, C.J.D., Warren, J.D., Ridha, B.H., et al., 2018. Effect of donepezil on transcranial magnetic stimulation parameters in Alzheimer's disease. Alzheimer's & Dementia: Translational Research & Clinical Interventions 4, 103–107.
Ilić, T.V., Korchounov, A., Ziemann, U., 2003. Methylphenidate facilitates and disinhibits the motor cortex in intact humans. Neuroreport 14, 773–776.
Ilić, T.V., Meintzschel, F., Cleff, U., Ruge, D., Kessler, K.R., Ziemann, U., 2002. Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J. Physiol. 545, 153–167.
Inghilleri, M., Conte, A., Frasca, V., Scaldaferri, N., Gilio, F., Santini, M., et al., 2006. Altered response to rTMS in patients with Alzheimer's disease. Clin. Neurophysiol. 117, 103–109.
Irlbacher, K., Brocke, J., Mechow, J.v., Brandt, S.A., 2007. Effects of GABA a and GABA B agonists on interhemispheric inhibition in man. Clin. Neurophysiol. 118, 308–316. https://doi.org/10.1016/j.clinph.2006.09.023.
Issac, T.G., Chandra, S.R., Nagaraju, B.C., 2013. Transcranial magnetic stimulation in patients with early cortical dementia: a pilot study. Ann. Indian Acad. Neurol. 16, 619–622.
Italia, M., Salvadè, M., La Greca, F., Zianni, E., Pelucchi, S., Spinola, A., et al., 2024. Anti-GluA3 autoantibodies define a new sub-population of frontotemporal lobar degeneration patients with distinct neuropathological features. Brain Behav. Immun. 118, 380–397. https://doi.org/10.1016/j.bbi.2024.03.018.
Jewett, G., Khayambashi, S., Frost, G.S., Beland, B., Lee, A., Hodgkinson, V., et al., 2022. Gold Coast criteria expand clinical trial eligibility in amyotrophic lateral sclerosis. Muscle Nerve 66, 397–403. https://doi.org/10.1002/mus.27660.
Johnsen, B., Pugdahl, K., Fuglsang-Frederiksen, A., Kollewe, K., Paracka, L., Dengler, R., et al., 2019. Diagnostic criteria for amyotrophic lateral sclerosis: a multicentre study of inter-rater variation and sensitivity. Clin. Neurophysiol. 130, 307–314. https://doi.org/10.1016/j.clinph.2018.11.021.
de Jongh, A.D., Braun, N., Weber, M., van Es, M.A., Masrori, P., Veldink, J.H., et al., 2022. Characterising ALS disease progression according to El Escorial and Gold Coast criteria. J. Neurol. Neurosurg. Psychiatry 93, 865–870. https://doi.org/10.1136/jnnp-2022-328823.
Julkunen, P., Jauhiainen, A.M., Könönen, M., Pääkkönen, A., Karhu, J., Soininen, H., 2011. Combining transcranial magnetic stimulation and electroencephalography may contribute to assess the severity of Alzheimer's disease. Int. J. Alzheimers Dis. 2011, 1–9.
Julkunen, P., Jauhiainen, A.M., Westerén-Punnonen, S., Pirinen, E., Soininen, H., Könönen, M., et al., 2008. Navigated TMS combined with EEG in mild cognitive impairment and Alzheimer's disease: a pilot study. J. Neurosci. Methods 172, 270–276. https://doi.org/10.1016/j.jneumeth.2008.04.021.

Kato, M., 1997. A study of magnetic stimulation in patients with clinically diagnosed corticobasal degeneration. Rinsho Shinkeigaku 37, 969–975.
Khademullah, C.S., Aqrabawi, A.J., Place, K.M., Dargaei, Z., Liang, X., Pressey, J.C., et al., 2020. Cortical interneuron-mediated inhibition delays the onset of amyotrophic lateral sclerosis. Brain 143, 800–810. https://doi.org/10.1093/brain/awaa034.
Khedr, E.M., Ahmed, M.A., Darwish, E.S., Ali, A.M., 2011. The relationship between motor cortex excitability and severity of Alzheimer's disease: a transcranial magnetic stimulation study. Neurophysiologie Clinique/Clinical Neurophysiology 41, 107–113.
Khedr, E.M., Lefaucheur, J.P., Hasan, A.M., Osama, K., 2021. Are there differences in cortical excitability between akinetic-rigid and tremor-dominant subtypes of Parkinson's disease? Neurophysiol. Clin. 51, 443–453. https://doi.org/10.1016/j.neucli.2021.08.002.
Khundakar, A.A., Hanson, P.S., Erskine, D., Lax, N.Z., Roscamp, J., Karyka, E., et al., 2016. Analysis of primary visual cortex in dementia with Lewy bodies indicates GABAergic involvement associated with recurrent complex visual hallucinations. Acta Neuropathol. Commun. 4, 66.
Kiernan, M.C., Vucic, S., Talbot, K., McDermott, C.J., Hardiman, O., Shefner, J.M., et al., 2021. Improving clinical trial outcomes in amyotrophic lateral sclerosis. Nat. Rev. Neurol. 17, 104–118. https://doi.org/10.1038/s41582-020-00434-z.
Knopman, D.S., Amieva, H., Petersen, R.C., Chételat, G., Holtzman, D.M., Hyman, B.T., et al., 2021. Alzheimer disease. Nat. Rev. Dis. Primers 7. https://doi.org/10.1038/s41572-021-00269-y.
Koch, G., Casula, E.P., Bonnì, S., Borghi, I., Assogna, M., Di Lorenzo, F., et al., 2025. Effects of 52 weeks of precuneus rTMS in Alzheimer's disease patients: a randomized trial. Alzheimer's Research and Therapy 17. https://doi.org/10.1186/s13195-025-01709-7.
Koch, G., Casula, E.P., Bonnì, S., Borghi, I., Assogna, M., Minei, M., et al., 2022. Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial. Brain 145, 3776–3786. https://doi.org/10.1093/brain/awac285.
Koch, G., Fernandez Del Olmo, M., Cheeran, B., Ruge, D., Schippling, S., Caltagirone, C., et al., 2007. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J. Neurosci. 27, 6815–6822.
Koch, G., Di Lorenzo, F., Bonnì, S., Ponzo, V., Caltagirone, C., Martorana, A., 2012. Impaired LTP- but not LTD-like cortical plasticity in Alzheimer's disease patients. J. Alzheimers Dis. 31, 593–599.
Koch, G., Di Lorenzo, F., igrave, S.B., Giacobbe, V., Bozzali, M., Caltagirone, C., et al., 2014. Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. Neuropsychopharmacology 1–8.
Koch, G., Di Lorenzo, F., Loizzo, S., Motta, C., Travaglione, S., Baiula, M., et al., 2017. CSF tau is associated with impaired cortical plasticity, cognitive decline and astrocyte survival only in APOE4-positive Alzheimer's disease. Sci. Rep. 7, 451.
Koch, G., Di Lorenzo, F., Del Olmo, M.F., Bonnì, S., Ponzo, V., Caltagirone, C., et al., 2016. Reversal of LTP-like cortical plasticity in Alzheimer's disease patients with tau-related faster clinical Progression. J. Alzheimers Dis. 50, 605–616.
Koch, G., Ponzo, V., Di Lorenzo, F., Caltagirone, C., Veniero, D., 2013. Hebbian and anti-hebbian spike-timing-dependent plasticity of human cortico-cortical connections. J. Neurosci. 33, 9725–9733.
Kojovic, M., Bologna, M., Kassavetis, P., Murase, N., Palomar, F.J., Berardelli, A., et al., 2012. Functional reorganization of sensorimotor cortex in early Parkinson disease. Neurology 78, 1441–1448.
Kojovic, M., Kassavetis, P., Bologna, M., Pareés, I., Rubio-Agusti, I., Beraredelli, A., et al., 2015. Transcranial magnetic stimulation follow-up study in early Parkinson's disease: a decline in compensation with disease progression? Mov. Disord. 30, 1098–1106. https://doi.org/10.1002/mds.26167.
Korchounov, A., Ziemann, U., 2011. Neuromodulatory neurotransmitters influence LTP-like plasticity in human cortex: a pharmaco-TMS study. Neuropsychopharmacology 36, 1894–1902. https://doi.org/10.1038/npp.2011.75.
Korner, S., Kollewe, K., Fahlbusch, M., Zapf, A., Dengler, R., Krampfl, K., et al., 2011. Onset and spreading patterns of upper and lower motor neuron symptoms in amyotrophic lateral sclerosis. Muscle Nerve 43, 636–642. https://doi.org/10.1002/mus.21936.
Kühn, A.A., Grosse, P., Holtz, K., Brown, P., Meyer, B.U., Kupsch, A., 2004. Patterns of abnormal motor cortex excitability in atypical parkinsonian syndromes. Clin. Neurophysiol. 115, 1786–1795.
Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., et al., 1993. Corticocortical inhibition in human motor cortex. J. Physiol. 471, 501–519.
Di Lazzaro, V., Bella, R., Benussi, A., Bologna, M., Borroni, B., Capone, F., et al., 2021. Diagnostic contribution and therapeutic perspectives of transcranial magnetic stimulation in dementia. Clin. Neurophysiol. 132, 2568–2607. https://doi.org/10.1016/j.clinph.2021.05.035.
Di Lazzaro, V., Oliviero, A., Mazzone, P., Pilato, F., Saturno, E., Insola, A., et al., 2002a. Direct demonstration of long latency cortico-cortical inhibition in normal subjects and in a patient with vascular parkinsonism. Clin. Neurophysiol. 113, 1673–1679. https://doi.org/10.1016/S1388-2457(02)00264-X.
Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., 2004. Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease. J. Neurol. 75, 555–559.
Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Marra, C., et al., 2005. Neurophysiological predictors of long term response to AChE inhibitors in AD patients. J. Neurol. Neurosurg. Psychiatry 76, 1064–1069. https://doi.org/10.1136/jnnp.2004.051334.
Di Lazzaro, V., Oliviero, A., Profice, P., Insola, A., Mazzone, P., Tonali, P., et al., 1999. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp. Brain Res. 124, 520–524. https://doi.org/10.1007/s002210050648.
Di Lazzaro, V., Oliviero, A., Profice, P., Pennisi, M.A., Di Giovanni, S., Zito, G., et al., 2000. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp. Brain Res. 135, 455–461.
Di Lazzaro, V., Oliviero, A., Profice, P., Saturno, E., Pilato, F., Insola, A., et al., 1998. Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control 109, 397–401. https://doi.org/10.1016/S0924-980X(98)00038-1.
Di Lazzaro, V., Oliviero, A., Tonali, P.A., Marra, C., Daniele, A., Profice, P., et al., 2002b. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. Neurology 59, 392–397.
Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Marra, C., Ranieri, F., et al., 2008. In vivo functional evaluation of central cholinergic circuits in vascular dementia. Clin. Neurophysiol. 119, 2494–2500.
Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Ranieri, F., Ricci, V., et al., 2007a. Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: a TMS study. Clin. Neurophysiol. 118, 2207–2214. https://doi.org/10.1016/j.clinph.2007.07.005.
Di Lazzaro, V., Pilato, F., Dileone, M., Saturno, E., Oliviero, A., Marra, C., et al., 2006. In vivo cholinergic circuit evaluation in frontotemporal and Alzheimer dementias. Neurology 66, 1111–1113.
Di Lazzaro, V., Pilato, F., Dileone, M., Saturno, E., Profice, P., Marra, C., et al., 2007b. Functional evaluation of cerebral cortex in dementia with Lewy bodies. Neuroimage 37, 422–429. https://doi.org/10.1016/j.neuroimage.2007.05.003.
Di Lazzaro, V., Rothwell, J.C., 2014. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J. Physiol. 592, 4115–4128.
Di Lazzaro, V., Ziemann, U., 2013. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. Front. Neural Circuits 7, 18.
Lee, H., Gunraj, C., Chen, R., 2007. The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex. J. Physiol. 580, 1021–1032. https://doi.org/10.1113/jphysiol.2006.126011.
Lee, K.D., Koo, J.H., Song, S.H., Jo, K.D., Lee, M.K., Jang, W., 2015. Central cholinergic dysfunction could be associated with oropharyngeal dysphagia in early Parkinson's disease. J. Neural Transm. 122, 1553–1561. https://doi.org/10.1007/s00702-015-1427-z.
Lefaucheur, J.P., 2009. Methods of therapeutic cortical stimulation. Neurophysiologie Clinique/Clinical Neurophysiology 39, 1–14.
Lefaucheur, J.P., Drouot, X., Von Raison, F., Ménard-Lefaucheur, I., Cesaro, P., Nguyen, J.P., 2004. Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin. Neurophysiol. 115, 2530–2541. https://doi.org/10.1016/j.clinph.2004.05.025.
Leiguarda, R.C., Merello, M., Nouzeilles, M.I., Balej, J., Rivero, A., Nogués, M., 2003. Limb-kinetic apraxia in corticobasal degeneration: clinical and kinematic features. Mov. Disord. 18, 49–59. https://doi.org/10.1002/mds.10303.
Leodori, G., De Bartolo, M.I., Piervincenzi, C., Mancuso, M., Ojha, A., Costanzo, M., et al., 2024. Mapping motor cortical network excitability and connectivity changes in de novo parkinson's disease. Mov. Disord. 39, 1523–1532. https://doi.org/10.1002/mds.29901.
Leodori, G., Belvisi, D., De Bartolo, M.I., Fabbrini, A., Costanzo, M., Vial, F., et al., 2020. Re-emergent tremor in parkinson's disease: the role of the motor cortex. Mov. Disord. 35, 1002–1011. https://doi.org/10.1002/mds.28022.
Leodori, G., Fabbrini, A., Suppa, A., Mancuso, M., Tikoo, S., Belvisi, D., et al., 2023. Effective connectivity abnormalities in Lewy body disease with visual hallucinations. Clin. Neurophysiol. 156, 156–165. https://doi.org/10.1016/j.clinph.2023.10.009.
Lewis, G.N., Byblow, W.D., 2002. Altered sensorimotor integration in Parkinson's disease. Brain 125, 2089–2099. https://doi.org/10.1093/brain/awf200.
Li, J.Y., Espay, A.J., Gunraj, C.A., Pal, P.K., Cunic, D.I., Lang, A.E., et al., 2007. Interhemispheric and ipsilateral connections in Parkinson's disease: Relation to mirror movements. Mov. Disord. 22, 813–821. https://doi.org/10.1002/mds.21386.
Li, S., Hong, S., Shepardson, N.E., Walsh, D.M., Shankar, G.M., Selkoe, D., 2009. Soluble oligomers of amyloid β protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. Neuron 62, 788–801. https://doi.org/10.1016/j.neuron.2009.05.012.
Liepert, J., Bär, K.J., Meske, U., Weiller, C., 2001. Motor cortex disinhibition in Alzheimer's disease. Clin. Neurophysiol. 112, 1436–1441.
Di Lorenzo, F., Martorana, A., Ponzo, V., Bonnì, S., D'Angelo, E., Caltagirone, C., et al., 2013. Cerebellar theta burst stimulation modulates short latency afferent inhibition in Alzheimer's disease patients. Front. Aging Neurosci. 5, 2.
Di Lorenzo, F., Motta, C., Bonnì, S., Mercuri, N.B., Caltagirone, C., Martorana, A., et al., 2018. LTP-like cortical plasticity is associated with verbal memory impairment in Alzheimer's disease patients. Brain Stimul. 12, 148–151. https://doi.org/10.1016/j.brs.2018.10.009.
Di Lorenzo, F., Ponzo, V., Bonnì, S., Motta, C., Negrão Serra, P.C., Bozzali, M., et al., 2016. Long-term potentiation-like cortical plasticity is disrupted in Alzheimer's disease patients independently from age of onset. Ann. Neurol. 80, 202–210.
Lu, C.S., Ikeda, A., Terada, K., Mima, T., Nagamine, T., Fukuyama, H., et al., 1998. Electrophysiological studies of early stage corticobasal degeneration. Mov. Disord. 13, 140–146. https://doi.org/10.1002/mds.870130126.
Lu, M.-K., Tsai, C.-H., Ziemann, U., 2012. Cerebellum to motor cortex paired associative stimulation induces bidirectional STDP-like plasticity in human motor cortex. Front. Hum. Neurosci. 6, 260. https://doi.org/10.3389/fnhum.2012.00260.
MacKinnon, C.D., Gilley, E.A., Weis-McNulty, A., Simuni, T., 2005. Pathways mediating abnormal intracortical inhibition in Parkinson's disease. Ann. Neurol. 58, 516–524.

Maekawa, S., Al-Sarraj, S., Kibble, M., Landau, S., Parnavelas, J., Cotter, D., et al., 2004. Cortical selective vulnerability in motor neuron disease: a morphometric study. Brain 127, 1237–1251. https://doi.org/10.1093/brain/awh132.
Mahapatra, R.K., Edwards, M.J., Schott, J.M., Bhatia, K.P., 2004. Corticobasal degeneration. Lancet Neurol. 3, 736–743. https://doi.org/10.1016/S1474-4422(04)00936-6.
Maidan, I., Zifman, N., Hausdorff, J.M., Giladi, N., Levy-Lamdan, O., Mirelman, A., 2021. A multimodal approach using TMS and EEG reveals neurophysiological changes in Parkinson's disease. Parkinsonism Relat. Disord. 89, 28–33. https://doi.org/10.1016/j.parkreldis.2021.06.018.
Maiella, M., Mencarelli, L., Casula, E.P., Borghi, I., Assogna, M., di Lorenzo, F., et al., 2024. Breakdown of TMS evoked EEG signal propagation within the default mode network in Alzheimer's disease. Clin. Neurophysiol. 167, 177–188. https://doi.org/10.1016/j.clinph.2024.09.007.
Manganelli, F., Vitale, C., Santangelo, G., Pisciotta, C., Iodice, R., Cozzolino, A., et al., 2009. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinsons disease. Brain 132, 2350–2355. https://doi.org/10.1093/brain/awp166.
De Marco, M., Venneri, A., 2018. Volume and connectivity of the ventral tegmental area are linked to neurocognitive signatures of Alzheimer's disease in humans. Journal of Alzheimer's Disease 63, 167–180. https://doi.org/10.3233/JAD-171018.
Marra, C., Quaranta, D., Profice, P., Pilato, F., Capone, F., Iodice, F., et al., 2012. Central cholinergic dysfunction measured "in vivo" correlates with different behavioral disorders in Alzheimer's disease and dementia with Lewy body. Brain Stimul. 5, 533–538. https://doi.org/10.1016/j.brs.2011.08.009.
Martorana, A., Di Lorenzo, F., Esposito, Z., Lo Giudice, T., Bernardi, G., Caltagirone, C., et al., 2013. Dopamine D_2-agonist rotigotine effects on cortical excitability and central cholinergic transmission in Alzheimer's disease patients. Neuropharmacology 64, 108–113.
Martorana, A., Mori, F., Esposito, Z., Kusayanagi, H., Monteleone, F., Codecà, C., et al., 2009. Dopamine modulates cholinergic cortical excitability in Alzheimer's disease patients. Neuropsychopharmacology 34, 2323–2328.
Martorana, A., Stefani, A., Palmieri, M.G., Esposito, Z., Bernardi, G., Sancesario, G., et al., 2008. L-dopa modulates motor cortex excitability in Alzheimer's disease patients. J. Neural Transm. 115, 1313–1319. https://doi.org/10.1007/s00702-008-0082-z.
Matamala, J.M., Howells, J., Dharmadasa, T., Trinh, T., Ma, Y., Lera, L., et al., 2018. Inter-session reliability of short-interval intracortical inhibition measured by threshold tracking TMS. Neurosci. Lett. 674, 18–23.
McDonnell, M.N., Orekhov, Y., Ziemann, U., 2006. The role of GABAB receptors in intracortical inhibition in the human motor cortex. Exp. Brain Res. 173, 86–93.
McKeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.-P., Weintraub, D., et al., 2017. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 89, 88–100.
McMackin, R., Bede, P., Pender, N., Hardiman, O., Nasseroleslami, B., 2019. Neurophysiological markers of network dysfunction in neurodegenerative diseases. Neuroimage Clin 22. https://doi.org/10.1016/j.nicl.2019.101706.
Menon, P., Geevasinga, N., van den Bos, M., Yiannikas, C., Kiernan, M.C., Vucic, S., 2017. Cortical hyperexcitability and disease spread in amyotrophic lateral sclerosis. Eur. J. Neurol. 24, 816–824.
Menon, P., Geevasinga, N., Yiannikas, C., Howells, J., Kiernan, M.C., Vucic, S., 2015. The sensitivity and specificity of threshold-tracking transcranial magnetic stimulation for the diagnosis of amyotrophic lateral sclerosis: a prospective study. Lancet Neurol. 14, 478–484.
Menon, P., Geevasinga, N., Yiannikas, C., Kiernan, M.C., Vucic, S., 2016. Cortical contributions to the flail leg syndrome: pathophysiological insights. Amyotroph Lateral Scler Frontotemporal Degener 17, 389–396. https://doi.org/10.3109/21678421.2016.1145232.
Menon, P., Kiernan, M.C., Vucic, S., 2014. Cortical dysfunction underlies the development of the split-hand in amyotrophic lateral sclerosis. PLoS One 9, e87124. https://doi.org/10.1371/journal.pone.0087124.
Menon, P., Yiannikas, C., Kiernan, M.C., Vucic, S., 2019. Regional motor cortex dysfunction in amyotrophic lateral sclerosis. Ann. Clin. Transl. Neurol. 6, 1373–1382. https://doi.org/10.1002/acn3.50819.
Merton, P.A., Morton, H.B., 1980. Stimulation of the cerebral cortex in the intact human subject. Nature 285, 227.
Mimura, Y., Nishida, H., Nakajima, S., Tsugawa, S., Morita, S., Yoshida, K., et al., 2021. Neurophysiological biomarkers using transcranial magnetic stimulation in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 121, 47–59. https://doi.org/10.1016/j.neubiorev.2020.12.003.
Morgante, F., Espay, A.J., Gunraj, C., Lang, A.E., Chen, R., 2006. Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. Brain 129, 1059–1069. https://doi.org/10.1093/brain/awl031.
Morita, Y., Osaki, Y., Doi, Y., 2008. Transcranial magnetic stimulation for differential diagnostics in patients with parkinsonism. Acta Neurol. Scand. 118, 159–163.
Moriyasu, S., Shimizu, T., Honda, M., Ugawa, Y., Hanajima, R., 2022. Motor cortical plasticity and its correlation with motor symptoms in Parkinson's disease. ENeurologicalSci 29. https://doi.org/10.1016/j.ensci.2022.100422.
Motta, C., Di Lorenzo, F., Ponzo, V., Pellicciari, M.C., Bonnì, S., Picazio, S., et al., 2018. Transcranial magnetic stimulation predicts cognitive decline in patients with Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 89, 1237–1242. https://doi.org/10.1136/jnnp-2017-317879.
Murakami, T., Abe, M., Tiksnadi, A., Nemoto, A., Futamura, M., Yamakuni, R., et al., 2024. Abnormal motor cortical plasticity as a useful neurophysiological biomarker for Alzheimer's disease pathology. Clin. Neurophysiol. 158, 170–179. https://doi.org/10.1016/j.clinph.2023.12.131.
Murley, A.G., Rouse, M.A., Jones, P.S., Ye, R., Hezemans, F.H., O'Callaghan, C., et al., 2020. GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. Brain. https://doi.org/10.1093/brain/awaa305.
Murley, A.G., Rowe, J.B., 2018. Neurotransmitter deficits from frontotemporal lobar degeneration. Brain 141, 1263–1285. https://doi.org/10.1093/brain/awx327.
Nakamura, H., Kitagawa, H., Kawaguchi, Y., Tsuji, H., 1997. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J. Physiol. 498 (Pt 3), 817–823.
Nardone, R., Bergmann, J., Brigo, F., Christova, M., Kunz, A., Seidl, M., et al., 2013. Functional evaluation of central cholinergic circuits in patients with Parkinson's disease and REM sleep behavior disorder: a TMS study. J. Neural Transm. 120, 413–422.
Nardone, R., Bergmann, J., Kronbichler, M., Kunz, A., Klein, S., Caleri, F., et al., 2008. Abnormal short latency afferent inhibition in early Alzheimer's disease: a transcranial magnetic demonstration. J. Neural Transm. 115, 1557–1562.
Nardone, R., Bratti, A., Tezzon, F., 2006. Motor cortex inhibitory circuits in dementia with Lewy bodies and in Alzheimer's disease. J. Neural Transm. 113, 1679–1684.
Nardone, R., Florio, I., Lochner, P., Tezzon, F., 2005. Cholinergic cortical circuits in Parkinson's disease and in progressive supranuclear palsy: a transcranial magnetic stimulation study. Exp. Brain Res. 163, 128–131.
Nardone, R., Höller, Y., Thomschewski, A., Kunz, A.B., Lochner, P., Golaszewski, S., et al., 2014a. Dopamine differently modulates central cholinergic circuits in patients with Alzheimer disease and CADASIL. J. Neural Transm. (Vienna) 121, 1313–1320.
Nardone, R., Tezzon, F., Höller, Y., Golaszewski, S., Trinka, E., Brigo, F., 2014b. Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease. Acta Neurol. Scand. 129, 351–366.
Neumann, M., Mackenzie, I.R.A., 2019. Review: Neuropathology of non-tau frontotemporal lobar degeneration. Neuropathol. Appl. Neurobiol. 45, 19–40. https://doi.org/10.1111/nan.12526.
Ni, Z., Bahl, N., Gunraj, C.A., Mazzella, F., Chen, R., 2013. Increased motor cortical facilitation and decreased inhibition in Parkinson disease. Neurology 80, 1746–1753.
Ni, Z., Gunraj, C., Kailey, P., Cash, R.F.H., Chen, R., 2014. Heterosynaptic modulation of motor cortical plasticity in human. J. Neurosci. 34, 7314–7321.
Ni, Z., Pinto, A.D., Lang, A.E., Chen, R., 2010. Involvement of the cerebellothalamocortical pathway in Parkinson disease. Ann. Neurol. 68, 816–824.
Nicholson, G.A., Howells, J., Kiernan, M.C., Ng, K., Vucic, S., Geevasinga, N., et al., 2015. Cortical function in asymptomatic carriers and patients with C9orf72 amyotrophic lateral sclerosis. JAMA Neurol. 72, 1268. https://doi.org/10.1001/jamaneurol.2015.1872.
Nihei, K., McKee, A.C., Kowall, N.W., 1993. Patterns of neuronal degeneration in the motor cortex of amyotrophic lateral sclerosis patients. Acta Neuropathol. 86, 55–64.
Niskanen, E., Könönen, M., Määttä, S., Hallikainen, M., Kivipelto, M., Casarotto, S., et al., 2011. New insights into alzheimer's disease progression: a combined TMS and structural MRI study. PLoS One 6, e26113.
Nobili, A., Latagliata, E.C., Viscomi, M.T., Cavallucci, V., Cutuli, D., Giacovazzo, G., et al., 2017. Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. Nat. Commun. 8. https://doi.org/10.1038/ncomms14727.
Oberman, L.M., Benussi, A., 2023. Transcranial magnetic stimulation across the lifespan: impact of developmental and degenerative processes. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2023.07.012.
Oh, E., Park, J., Youn, J., Kim, J.-S., Park, S., Jang, W., 2017. Olfactory dysfunction in early Parkinson's disease is associated with short latency afferent inhibition reflecting central cholinergic dysfunction. Clin. Neurophysiol. 128, 1061–1068.
Okkels, N., Grothe, M.J., Taylor, J.P., Hasselbalch, S.G., Fedorova, T.D., Knudsen, K., et al., 2024. Cholinergic changes in Lewy body disease: implications for presentation, progression and subtypes. Brain 147, 2308–2324. https://doi.org/10.1093/brain/awae069.
Okuma, Y., Urabe, T., Mochizuki, H., Miwa, H., Shimo, Y., Mori, H., et al., 2000. Asymmetric cortico-cortical inhibition in patients with progressive limb-kinetic apraxia. Acta Neurol. Scand. 102, 244–248.
Olazarán, J., Hernández-Tamames, J.A., Molina, E., García-Polo, P., Dobato, J.L., Álvarez-Linera, J., et al., 2013. Clinical and anatomical correlates of gait dysfunction in Alzheimer's disease. J. Alzheimers Dis. 33, 495–505.
Olazarán, J., Prieto, J., Cruz, I., Esteban, A., 2010. Cortical excitability in very mild Alzheimer's disease: a long-term follow-up study. J. Neurol. 257, 2078–2085.
Olğun, Y., Aksoy Poyraz, C., Bozluolçay, M., Gündüz, A., Poyraz, B.Ç., 2024. A comparative transcranial magnetic stimulation study: Assessing cortical excitability and plasticity in Alzheimer's disease, dementia with Lewy bodies and Frontotemporal dementia. Psychogeriatrics 24, 272–280. https://doi.org/10.1111/psyg.13070.
Oliveri, M., Koch, G., Torriero, S., Caltagirone, C., 2005. Increased facilitation of the primary motor cortex following 1 Hz repetitive transcranial magnetic stimulation of the contralateral cerebellum in normal humans. Neurosci. Lett. 376, 188–193. https://doi.org/10.1016/j.neulet.2004.11.053.
Otani, R., Shibuya, K., Shimizu, T., Kitaoji, T., Noto, Y.I., Bokuda, K., et al., 2024. Diagnostic utility of Gold Coast criteria for amyotrophic lateral sclerosis in Asia. Amyotroph Lateral Scler Frontotemporal Degener 25, 264–270. https://doi.org/10.1080/21678421.2024.2303062.
Padovani, A., Benussi, A., Cantoni, V., Dell'Era, V., Cotelli, M.S., Caratozzolo, S., et al., 2018. Diagnosis of mild cognitive impairment due to alzheimer's disease with transcranial magnetic stimulation. J. Alzheimers Dis. 65, 221–230. https://doi.org/10.3233/JAD-180293.
Padovani, A., Benussi, A., Cotelli, M.S., Ferrari, C., Cantoni, V., Dell'Era, V., et al., 2019. Transcranial magnetic stimulation and amyloid markers in mild cognitive

impairment: impact on diagnostic confidence and diagnostic accuracy. Alzheimers Res. Ther. 11, 95. https://doi.org/10.1186/s13195-019-0555-3.
Pal, P.K., Gunraj, C.A., Li, J.Y., Lang, A.E., Chen, R., 2008. Reduced intracortical and interhemispheric inhibitions in corticobasal syndrome. J. Clin. Neurophysiol. 25, 304–312.
Palese, F., Bonomi, E., Nuzzo, T., Benussi, A., Mellone, M., Zianni, E., et al., 2020. Anti-GluA3 antibodies in frontotemporal dementia: effects on glutamatergic neurotransmission and synaptic failure. Neurobiol. Aging 86, 143–155. https://doi.org/10.1016/j.neurobiolaging.2019.10.015.
Palop, J.J., Mucke, L., 2010. Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat. Neurosci. 13, 812–818.
Paparella, I., Cardone, P., Zanichelli, B., Lamalle, L., Collette, F., Sherif, S., et al., 2025. 7 Tesla magnetic resonance spectroscopy estimates of GABA concentration relate to physiological measures of tonic inhibition in the human motor cortex 2822 I. Paparella and others. J Physiol 603, 2821–2838. https://doi.org/10.1113/JP287311#support-information-section.
Pascual-Leone, A., Valls-Solé, J., Wassermann, E.M., Hallett, M., 1994. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117, 847–858. https://doi.org/10.1093/brain/117.4.847.
Passera, B., Harquel, S., Chauvin, A., Gérard, P., Lai, L., Moro, E., et al., 2023. Multi-scale and cross-dimensional TMS mapping: a proof of principle in patients with Parkinson's disease and deep brain stimulation. Front. Neurosci. 17. https://doi.org/10.3389/fnins.2023.1004763.
Paulus, W., Rothwell, J.C., 2016. Membrane resistance and shunting inhibition: where biophysics meets state-dependent human neurophysiology. J. Physiol. 594, 2719–2728.
Pavey, N., Hannaford, A., Van Den Bos, M., Kiernan, M.C., Menon, P., Vucic, S., 2024. Distinct neuronal circuits mediate cortical hyperexcitability in amyotrophic lateral sclerosis. Brain 147, 2344–2356. https://doi.org/10.1093/brain/awae049.
Pavey, N., Menon, P., van den Bos, M.A.J., Kiernan, M.C., Vucic, S., 2023. Cortical inhibition and facilitation are mediated by distinct physiological processes. Neurosci. Lett. 803, 137191. https://doi.org/10.1016/j.neulet.2023.137191.
Pelosin, E., Ogliastro, C., Lagravinese, G., Bonassi, G., Mirelman, A., Hausdorff, J.M., et al., 2016. Attentional control of gait and falls: is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? Front. Aging Neurosci. 8. https://doi.org/10.3389/fnagi.2016.00104.
Pepin, J.L., Bogacz, D., de Pasqua, V., Delwaide, P.J., 1999. Motor cortex inhibition is not impaired in patients with Alzheimer's disease: evidence from paired transcranial magnetic stimulation. J. Neurol. Sci. 170, 119–123.
Perellón-Alfonso, R., Abellaneda-Pérez, K., Pileckyte, I., Cabello-Toscano, M., Mulet-Pons, L., Vaqué-Alcázar, L., et al., 2024. Spontaneous and perturbation-based EEG cortical excitability markers are associated with plasma p-tau181 concentration in healthy middle-aged adults. Heliyon 10. https://doi.org/10.1016/j.heliyon.2024.e41118.
Petkau, T.L., Neal, S.J., Milnerwood, A., Mew, A., Hill, A.M., Orban, P., et al., 2012. Synaptic dysfunction in progranulin-deficient mice. Neurobiol. Dis. 45, 711–722.
Petri S, Krampfl K, Hashemi F, Grothe C, Hori A, Dengler R, et al. Distribution of GABA A Receptor mRNA in the Motor Cortex of ALS Patients. vol. 62. 2003.
Peurala, S.H., M Müller-Dahlhaus, J.F., Arai, N., Ziemann, U., 2008. Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF). Clin. Neurophysiol. 119, 2291–2297.
Pierantozzi, M., Panella, M., Palmieri, M.G., Koch, G., Giordano, A., Marciani, M.G., et al., 2004. Different TMS patterns of intracortical inhibition in early onset Alzheimer dementia and frontotemporal dementia. Clin. Neurophysiol. 115, 2410–2418.
Pigorini, A., Casali, A.G., Casarotto, S., Ferrarelli, F., Baselli, G., Mariotti, M., et al., 2011. Time-frequency spectral analysis of TMS-evoked EEG oscillations by means of Hilbert-Huang transform. J. Neurosci. Methods 198, 236–245. https://doi.org/10.1016/j.jneumeth.2011.04.013.
Pilotto, A., Gazzina, S., Benussi, A., Manes, M., Dell'Era, V., Cristillo, V., et al., 2017. Mild cognitive impairment and progression to dementia in progressive supranuclear palsy. Neurodegener Dis 17, 286–291. https://doi.org/10.1159/000479110.
Pinto, A.D., Chen, R., 2001. Suppression of the motor cortex by magnetic stimulation of the cerebellum. Exp. Brain Res. 140, 505–510. https://doi.org/10.1007/s002210100862.
Postuma, R.B., Poewe, W., Litvan, I., Lewis, S., Lang, A.E., Halliday, G., et al., 2018. Validation of the MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30, 1591.
Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., et al., 2014. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J. Neurosci. 34, 5603–5612.
Pugdahl, K., Camdessanché, J.P., Cengiz, B., de Carvalho, M., Liguori, R., Rossatto, C., et al., 2021. Gold Coast diagnostic criteria increase sensitivity in amyotrophic lateral sclerosis. Clin. Neurophysiol. 132, 3183–3189. https://doi.org/10.1016/j.clinph.2021.08.014.
Pun, S., Santos, A.F., Saxena, S., Xu, L., Caroni, P., 2006. Selective vulnerability and pruning of phasic motoneuron axons in motoneuron disease alleviated by CNTF. Nat. Neurosci. 9, 408–419.
Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134, 2456–2477. https://doi.org/10.1093/brain/awr179.
Ravits, J., Paul, P., Jorg, C., 2007. Focality of upper and lower motor neuron degeneration at the clinical onset of ALS. Neurology 68, 1571–1575.
Ravits, J.M., La Spada, A.R., 2009. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. Neurology 73, 805–811. https://doi.org/10.1212/WNL.0b013e3181b6bbbd.
Reale, L.A., Dyer, M.S., Perry, S.E., Young, K.M., Dickson, T.C., Woodhouse, A., et al., 2023. Pathologically mislocalised TDP-43 in upper motor neurons causes a die-forward spread of ALS-like pathogenic changes throughout the mouse corticomotor system. Prog. Neurobiol. 226, 102449. https://doi.org/10.1016/j.pneurobio.2023.102449.
Ridding, M.C., Inzelberg, R., Rothwell, J.C., 1995. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann. Neurol. 37, 181–188.
Rizzardi, A., Benussi, A., Zatti, C., Tirloni, C., Agostini, N., Foresti, G., et al., 2025. Cortical inhibitory and facilitatory alterations in the continuum of alpha-synucleinopathies. Clin. Neurophysiol. 178, 2110938. https://doi.org/10.1016/j.clinph.2025.2110938.
Rizzo, V., Siebner, H.R., Morgante, F., Mastroeni, C., Girlanda, P., Quartarone, A., 2009. Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a hebbian mechanism. Cereb. Cortex 19, 907–915. https://doi.org/10.1093/cercor/bhn144.
Rochester, L., Yarnall, A.J., Baker, M.R., David, R.V., Lord, S., Galna, B., et al., 2012. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. Brain 135, 2779–2788. https://doi.org/10.1093/brain/aws207.
Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., Massimini, M., 2009. Natural frequencies of human corticothalamic circuits. J. Neurosci. 29, 7679–7685. https://doi.org/10.1523/JNEUROSCI.0445-09.2009.
Rose, S., Rowland, T., Pannek, K., Baumann, F., Coulthard, A., McCombe, P., et al., 2012. Structural hemispheric asymmetries in the human precentral gyrus hand representation. Neuroscience 210, 211–221. https://doi.org/10.1016/j.neuroscience.2012.02.044.
Rossini, P.M., Burke, D., Chen, R., Cohen, L.G., Daskalakis, Z., Di Iorio, R., et al., 2015. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. an updated report from an I.F.C.N Committee. Clin. Neurophysiol. 126, 1071–1107.
Rossini, P.M., Miraglia, F., Alù, F., Cotelli, M., Ferreri, F., Di Iorio, R., et al., 2020. Neurophysiological hallmarks of neurodegenerative cognitive decline: the study of brain connectivity as a biomarker of early dementia. J Pers Med 10. https://doi.org/10.3390/jpm10020034.
Rusu, C.V., Murakami, M., Ziemann, U., Triesch, J., 2014. A model of TMS-induced I-waves in motor cortex. Brain Stimul. 7, 401–414. https://doi.org/10.1016/j.brs.2014.02.009.
Saez-Atienzar, S., Bandres-Ciga, S., Langston, R.G., Kim, J.J., Choi, S.W., Reynolds, R.H., et al., 2021. Genetic analysis of amyotrophic lateral sclerosis identifies contributing pathways and cell types. Sci. Adv. 7. https://doi.org/10.1126/sciadv.abd9036.
Sailer, A., Molnar, G.F., Paradiso, G., Gunraj, C.A., Lang, A.E., Chen, R., 2003. Short and long latency afferent inhibition in Parkinson's disease. Brain 126, 1883–1894. https://doi.org/10.1093/brain/awg183.
Sanger, T.D., Garg, R.R., Chen, R., 2001. Interactions between two different inhibitory systems in the human motor cortex. J. Physiol. 530, 307–317.
Santos Silva, C., Pavey, N., Calma, A.D., Kiernan, M.C., Menon, P., van den Bos, M., et al., 2025. Utility of cortical inhibitory and facilitatory neuronal circuits in amyotrophic lateral sclerosis diagnosis. Eur. J. Neurol. 32, e70203. https://doi.org/10.1111/ene.70203.
Saravanamuttu, J., Radhu, N., Udupa, K., Baarbé, J., Gunraj, C., Chen, R., 2021. Impaired motor cortical facilitatory-inhibitory circuit interaction in Parkinson's disease. Clin. Neurophysiol. 132, 2685–2692. https://doi.org/10.1016/j.clinph.2021.05.032.
Schanz, O., Bageac, D., Braun, L., Traynor, B., Lehky, T.J., Floeter, M.K., 2016. Cortical hyperexcitability in patients with C9orf72 mutations: relationship to phenotype. Muscle Nerve.
Scheltens, P., Blennow, K., Breteler, M.M.B., De Strooper, B., Frisoni, G.B., Salloway, S., et al., 2016. Alzheimer's disease. Lancet 388, 505–517.
Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., et al., 2021. Alzheimer's disease. Lancet 397, 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4.
Schilberg, L., Schuhmann, T., Sack, A.T., 2017. Interindividual variability and intraindividual reliability of intermittent theta burst stimulation-induced neuroplasticity mechanisms in the healthy brain. J. Cogn. Neurosci. 29, 1022–1032. https://doi.org/10.1162/jocn_a_01100.
Schirinzi, T., Di Lorenzo, F., Sancesario, G.M., Di Lazzaro, G., Ponzo, V., Pisani, A., et al., 2018. Amyloid-mediated cholinergic dysfunction in motor impairment related to Alzheimer's disease. J. Alzheimers Dis. 64, 525–532.
Schöll, M., Verberk, I.M.W., del Campo, M., Delaby, C., Therriault, J., Chong, J.R., et al., 2024. Challenges in the practical implementation of blood biomarkers for Alzheimer's disease. Lancet Healthy Longev 5. https://doi.org/10.1016/j.lanhl.2024.07.013.
Schulz-Schaeffer, W.J., 2010. The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol. 120, 131–143. https://doi.org/10.1007/s00401-010-0711-0.
Schumacher, J., Peraza, L.R., Firbank, M., Thomas, A.J., Kaiser, M., Gallagher, P., et al., 2019. Dysfunctional brain dynamics and their origin in Lewy body dementia. Brain. https://doi.org/10.1093/brain/awz069.
Shafi, M.M., Brandon Westover, M., Oberman, L., Cash, S.S., Pascual-Leone, A., 2014. Modulation of EEG functional connectivity networks in subjects undergoing repetitive transcranial magnetic stimulation. Brain Topogr. 27, 172–191. https://doi.org/10.1007/s10548-013-0277-y.
Shankar, G.M., Li, S., Mehta, T.H., Garcia-Munoz, A., Shepardson, N.E., Smith, I., et al., 2008. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair

synaptic plasticity and memory. Nat. Med. 14, 837–842. https://doi.org/10.1038/nm1782.
Shefner, J.M., Al-Chalabi, A., Baker, M.R., Cui, L.Y., de Carvalho, M., Eisen, A., et al., 2020. A proposal for new diagnostic criteria for ALS. Clin. Neurophysiol. 131, 1975–1978. https://doi.org/10.1016/j.clinph.2020.04.005.
Shen, D., Yang, X., Wang, Y., He, D., Sun, X., Cai, Z., et al., 2021. The Gold Coast criteria increases the diagnostic sensitivity for amyotrophic lateral sclerosis in a chinese population. Transl Neurodegener 10, 28. https://doi.org/10.1186/s40035-021-00253-2.
Shibuya, K., Simon, N.G., Geevasinga, N., Menon, P., Howells, J., Park, S.B., et al., 2017. The evolution of motor cortical dysfunction in amyotrophic lateral sclerosis. Clin. Neurophysiol. 128, 1075–1082.
Shirota, Y., Hamada, M., Hanajima, R., Terao, Y., Matsumoto, H., Ohminami, S., et al., 2010. Cerebellar dysfunction in progressive supranuclear palsy: a transcranial magnetic stimulation study. Mov. Disord. 25, 2413–2419.
Shirota, Y., Ohminami, S., Tsutsumi, R., Terao, Y., Ugawa, Y., Tsuji, S., et al., 2019. Increased facilitation of the primary motor cortex in de novo Parkinson's disease. Parkinsonism Relat. Disord. 66, 125–129. https://doi.org/10.1016/j.parkreldis.2019.07.022.
Sims, J.R., Zimmer, J.A., Evans, C.D., Lu, M., Ardayfio, P., Sparks, J.D., et al., 2023. Donanemab in early symptomatic Alzheimer Disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. J. Am. Med. Assoc. 330, 512–527. https://doi.org/10.1001/jama.2023.13239.
Small, S.L., 2025. Precision neurology. Ageing Res. Rev. 104. https://doi.org/10.1016/j.arr.2024.102632.
Spagnolo, F., Coppi, E., Chieffo, R., Straffi, L., Fichera, M., Nuara, A., et al., 2013. Interhemispheric balance in parkinson's disease: a transcranial magnetic stimulation study. Brain Stimul. 6, 892–897.
Spillantini, M.G., Goedert, M., 2013. Tau pathology and neurodegeneration. Lancet Neurol. 12, 609–622.
Di Stasio, F., Suppa, A., Fabbrini, A., Marsili, L., Asci, F., Conte, A., et al., 2018. Parkinsonism is associated with altered primary motor cortex plasticity in frontotemporal dementia-primary progressive aphasia variant. Neurobiol. Aging 69, 230–238. https://doi.org/10.1016/j.neurobiolaging.2018.05.026.
Steele, J.C., Richardson, G.J., Olszewski, J., 1964. Progressive supranuclear palsy. a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch. Neurol. 10, 333–359.
Steinmetz, J.D., Seeher, K.M., Schiess, N., Nichols, E., Cao, B., Servili, C., et al., 2024. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 23, 344–381. https://doi.org/10.1016/S1474-4422(24)00038-3.
Stikvoort García, D.J.L., Sleutjes, B., van Schelven, L.J., Goedee, H.S., van den Berg, L.H., 2023. Diagnostic accuracy of nerve excitability and compound muscle action potential scan derived biomarkers in amyotrophic lateral sclerosis. Eur. J. Neurol. 30, 3068–3078. https://doi.org/10.1111/ene.15954.
Suppa, A., Asci, F., Kamble, N., Chen, K.H., Sciacca, G., Merchant, S.H.I., et al., 2025. Neurophysiology of atypical parkinsonian syndromes: a study group position paper. Mov. Disord. https://doi.org/10.1002/mds.30225.
Suppa, A., Quartarone, A., Siebner, H.R., Chen, R., Di Lazzaro, V., Del Giudice, P., et al., 2017. The associative brain at work: evidence from paired associative stimulation studies in humans. Clin. Neurophysiol. 128, 2140–2164.
Suppa, A., Di Stasio, F., Marsili, L., Upadhyay, N., Belvisi, D., Conte, A., et al., 2016. Primary motor cortex LTP/LTD-like plasticity in probable corticobasal syndrome. J. Neurophysiol. 115, 717–727.
Suzuki, Y.I., Shibuya, K., Misawa, S., Suichi, T., Tsuneyama, A., Kojima, Y., et al., 2022. Relationship between motor cortical and peripheral axonal hyperexcitability in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2021-328550.
Swash, M., 2012. Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? J. Neurol. Neurosurg. Psychiatry 83, 659–662. https://doi.org/10.1136/jnnp-2012-302315.
Tankisi, H., Cengiz, B., Howells, J., Samusyte, G., Koltzenburg, M., Bostock, H., 2021a. Short-interval intracortical inhibition as a function of inter-stimulus interval: three methods compared. Brain Stimul 14, 22–32. https://doi.org/10.1016/j.brs.2020.11.002.
Tankisi, H., Nielsen, C.S., Howells, J., Cengiz, B., Samusyte, G., Koltzenburg, M., et al., 2021. Early diagnosis of amyotrophic lateral sclerosis by threshold tracking and conventional transcranial magnetic stimulation. Eur. J. Neurol. 28, 3030–3039. https://doi.org/10.1111/ene.15010.
Tankisi, H., Pia, H., Strunge, K., Howells, J., Cengiz, B., Samusyte, G., et al., 2022. Three different short-interval intracortical inhibition methods in early diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 1–9. https://doi.org/10.1080/21678421.2022.2101926.
Tautan, A.M., Casula, E., Borghi, I., Maiella, M., Bonni, S., Minei, M., et al., 2022. Characterizing TMS-EEG perturbation indexes using signal energy: initial study on Alzheimer's disease classification. Institute of Electrical and Electronics Engineers Inc., pp. 398–401, 10.1109/EMBC48229.2022.9871043.
Tăuţan, A.M., Casula, E.P., Pellicciari, M.C., Borghi, I., Maiella, M., Bonni, S., et al., 2023. TMS-EEG perturbation biomarkers for Alzheimer's disease patients classification. Sci. Rep. 13. https://doi.org/10.1038/s41598-022-22978-4.
Terranova, C., Carmen, T., Sant'Angelo, A., Antonino, S., Morgante, F., Francesca, M., et al., 2013. Impairment of sensory-motor plasticity in mild Alzheimer's disease. Brain Stimul. 6, 62–66.
Teunissen, C.E., Verberk, I.M.W., Thijssen, E.H., Vermunt, L., Hansson, O., Zetterberg, H., et al., 2022. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol. 21, 66–77. https://doi.org/10.1016/S1474-4422(21)00361-6.
Thut, G., Pascual-Leone, A., 2010. Editorial: Integrating TMS with EEG: how and what for? Brain Topogr. 22, 215–218. https://doi.org/10.1007/s10548-009-0128-z.
Tokimura, H., Di Lazzaro, V., Tokimura, Y., Oliviero, A., Profice, P., Insola, A., et al., 2000. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J. Physiol. 523 (Pt 2), 503–513.
Trebbastoni, A., Gilio, F., D'Antonio, F., Cambieri, C., Ceccanti, M., de Lena, C., et al., 2012. Chronic treatment with rivastigmine in patients with Alzheimer's disease: a study on primary motor cortex excitability tested by 5Hz-repetitive transcranial magnetic stimulation. Clin. Neurophysiol. 123, 902–909.
Tremblay, F., Tremblay, L.E., 2002. Cortico-motor excitability of the lower limb motor representation: a comparative study in Parkinson's disease and healthy controls. Clin. Neurophysiol. 113, 2006–2012. https://doi.org/10.1016/s1388-2457(02)00301-2.
Tremblay, S., Rogasch, N.C., Premoli, I., Blumberger, D.M., Casarotto, S., Chen, R., et al., 2019. Clinical utility and prospective of TMS-EEG. Clin. Neurophysiol. 130, 802–844. https://doi.org/10.1016/j.clinph.2019.01.001.
Tremblay, S., Vernet, M., Bashir, S., Pascual-Leone, A., Théoret, H., 2015. Theta burst stimulation to characterize changes in brain plasticity following mild traumatic brain injury: a proof-of-principle study. Restor. Neurol. Neurosci. 33, 611–620. https://doi.org/10.3233/RNN-140459.
Trompetto, C., Buccolieri, A., Marchese, R., Marinelli, L., Michelozzi, G., Abbruzzese, G., 2003. Impairment of transcallosal inhibition in patients with corticobasal degeneration. Clin. Neurophysiol. 114, 2181–2187.
Turner, M.R., Hammers, A., Al-Chalabi, A., Shaw, C.E., Andersen, P.M., Brooks, D.J., et al., 2005. Distinct cerebral lesions in sporadic and "D90A" SOD1 ALS: Studies with [11C]flumazenil PET. Brain 128, 1323–1329. https://doi.org/10.1093/brain/awh509.
Turner, M.R., Wicks, P., Brownstein, C.A., Massagli, M.P., Toronjo, M., Talbot, K., et al., 2011. Concordance between site of onset and limb dominance in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 82, 853–854. https://doi.org/10.1136/jnnp.2010.208413.
Tveit, J., Aurlien, H., Plis, S., Calhoun, V.D., Tatum, W.O., Schomer, D.L., et al., 2023. Automated interpretation of clinical electroencephalograms using artificial intelligence. JAMA Neurol. 80, 805–812. https://doi.org/10.1001/jamaneurol.2023.1645.
Ueki, Y., Mima, T., Kotb, M.A., Sawada, H., Saiki, H., Ikeda, A., et al., 2006. Altered plasticity of the human motor cortex in Parkinson's disease. Ann. Neurol. 59, 60–71. https://doi.org/10.1002/ana.20692.
Ugawa, Y., Uesaka, Y., Terao, Y., Hanajima, R., Kanazawa, I., 1995. Magnetic stimulation over the cerebellum in humans. Ann. Neurol. 37, 703–713. https://doi.org/10.1002/ana.410370603.
Valls-Solé, J., Pascual-Leone, A., Brasil-Neto, J.P., Cammarota, A., McShane, L., Hallett, M., 1994. Abnormal facilitation of the response to transcranial magnetic stimulation in patients with Parkinson's disease. Neurology 44, 735–741. https://doi.org/10.1212/wnl.44.4.735.
Valls-Solé, J., Pascual-Leone, A., Wassermann, E.M., Hallett, M., 1992. Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr. Clin. Neurophysiol. 85, 355–364.
Valls-Solé, J., Tolosa, E., Marti, M.J., Valldeoriola, F., Revilla, M., Pastor, P., et al., 2001. Examination of motor output pathways in patients with corticobasal ganglionic degeneration using transcranial magnetic stimulation. Brain 124, 1131–1137. https://doi.org/10.1093/brain/124.6.1131.
Valzania, F., Strafella, A.P., Quatrale, R., Santangelo, M., Tropeani, A., Lucchi, D., et al., 1997. Motor evoked responses to paired cortical magnetic stimulation in Parkinson's disease. Electroencephalogr. Clin. Neurophysiol. 105, 37–43. https://doi.org/10.1016/s0924-980x(96)96517-0.
Vernet, M., Bashir, S., Yoo, W.K., Oberman, L., Mizrahi, I., Ifert-Miller, F., et al., 2014. Reproducibility of the effects of theta burst stimulation on motor cortical plasticity in healthy participants. Clin. Neurophysiol. 125, 320–326. https://doi.org/10.1016/j.clinph.2013.07.004.
Versace, V., Langthaler, P.B., Sebastianelli, L., Höller, Y., Brigo, F., Orioli, A., et al., 2017. Impaired cholinergic transmission in patients with Parkinson's disease and olfactory dysfunction. J. Neurol. Sci. 377, 55–61.
Vucic, S., Cheah, B.C., Kiernan, M.C., 2011. Dissecting the mechanisms underlying short-interval intracortical inhibition using exercise. Cereb. Cortex 21, 1639–1644. https://doi.org/10.1093/cercor/bhq235.
Vucic, S., Cheah, B.C., Krishnan, A.V., Burke, D., Kiernan, M.C., 2009. The effects of alterations in conditioning stimulus intensity on short interval intracortical inhibition. Brain Res. 1273, 39–47.
Vucic, S., Cheah, B.C., Yiannikas, C., Kiernan, M.C., 2011. Cortical excitability distinguishes ALS from mimic disorders. Clin. Neurophysiol. 122, 1860–1866. https://doi.org/10.1016/j.clinph.2010.12.062.
Vucic, S., Higashihara, M., Sobue, G., Atsuta, N., Doi, Y., Kuwabara, S., et al., 2020. ALS is a multistep process in South Korean, Japanese, and Australian patients. Neurology 94, e1657–e1663. https://doi.org/10.1212/WNL.0000000000009015.
Vucic, S., Kiernan, M.C., 2017. Transcranial magnetic stimulation for the assessment of neurodegenerative disease. Neurotherapeutics 14, 91–106. https://doi.org/10.1007/s13311-016-0487-6.
Vucic, S., Kiernan, M.C., 2008. Cortical excitability testing distinguishes Kennedy's disease from amyotrophic lateral sclerosis. Clin. Neurophysiol. 119, 1088–1096. https://doi.org/10.1016/j.clinph.2008.01.011.
Vucic, S., Kiernan, M.C., 2007. Abnormalities in cortical and peripheral excitability in flail arm variant amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 78, 849–852. https://doi.org/10.1136/jnnp.2006.105056.

Vucic, S., Kiernan, M.C., 2006. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. Brain 129, 2436–2446. https://doi.org/10.1093/brain/awl172.
Vucic, S., Lin, C.-S.-Y., Cheah, B.C., Murray, J., Menon, P., Krishnan, A.V., et al., 2013a. Riluzole exerts central and peripheral modulating effects in amyotrophic lateral sclerosis. Brain 136, 1361–1370. https://doi.org/10.1093/brain/awt085.
Vucic, S., Nicholson, G.A., Kiernan, M.C., 2010. Cortical excitability in hereditary motor neuronopathy with pyramidal signs: comparison with ALS. J. Neurol. Neurosurg. Psychiatry 81, 97–100.
Vucic, S., Nicholson, G.A., Kiernan, M.C., 2008. Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. Brain 131, 1540–1550. https://doi.org/10.1093/brain/awn071.
Vucic, S., Pavey, N., Menon, P., Babayev, M., Maslyukova, A., Muraviev, A., et al., 2025. Neurophysiological assessment of cortical motor function: a direct comparison of methodologies. Clin. Neurophysiol. 170, 14–21. https://doi.org/10.1016/j.clinph.2024.12.001.
Vucic, S., Rothstein, J.D., Kiernan, M.C., 2014. Advances in treating amyotrophic lateral sclerosis: insights from pathophysiological studies. Trends Neurosci. 37, 433–442. https://doi.org/10.1016/j.tins.2014.05.006.
Vucic, S., Stanley Chen, K.H., Kiernan, M.C., Hallett, M., Benninger, D.H., Di Lazzaro, V., et al., 2023. Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee. Clin. Neurophysiol. 150, 131–175. https://doi.org/10.1016/j.clinph.2023.03.010.
Vucic, S., Westeneng, H.J., Al-Chalabi, A., Van Den Berg, L.H., Talman, P., Kiernan, M.C., 2019. Amyotrophic lateral sclerosis as a multi-step process: an Australia population study. Amyotroph Lateral Scler Frontotemporal Degener 20, 532–537. https://doi.org/10.1080/21678421.2018.1556697.
Vucic, S., Ziemann, U., Eisen, A., Hallett, M., Kiernan, M.C., 2013b. Transcranial magnetic stimulation and amyotrophic lateral sclerosis: pathophysiological insights. J. Neurol. Neurosurg. Psychiatry 84, 1161–1170.
Wagle-Shukla, A., Ni, Z., Gunraj, C.A., Bahl, N., Chen, R., 2009. Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. J. Physiol. 587, 5665–5678.
Walsh, D.M., Klyubin, I., Fadeeva, J.V., Cullen, W.K., Anwyl, R., Wolfe, M.S., et al., 2002. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416, 535–539.
Wang, P., Zhang, H., Han, L., Zhou, Y., 2016. Cortical function in Alzheimer's disease and frontotemporal dementia. Transl. Neurosci. 7, 116–125.
Wegrzyn, M., Teipel, S.J., Oltmann, I., Bauer, A., Thome, J., Großmann, A., et al., 2013. Structural and functional cortical disconnection in Alzheimer's disease: a combined study using diffusion tensor imaging and transcranial magnetic stimulation. Psychiatry Res. Neuroimaging 212, 192–200.
Werhahn, K.J., Kunesch, E., Noachtar, S., Benecke, R., Classen, J., 1999. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J. Physiol. 517 (Pt 2), 591–597.
Wicks, P., Turner, M.R., Abrahams, S., Hammers, A., Brooks, D.J., Leigh, P.N., et al., 2008. Neuronal loss associated with cognitive performance in amyotrophic lateral sclerosis: an (11 C)-flumazenil PET study. Amyotroph. Lateral Scler. 9, 43–49. https://doi.org/10.1080/17482960701737716.
Williams, K.L., Fifita, J.A., Vucic, S., Durnall, J.C., Kiernan, M.C., Blair, I.P., et al., 2013. Pathophysiological insights into ALS with C9ORF72 expansions. J. Neurol. Neurosurg. Psychiatry 84, 931–935.
Williamson, T.L., Cleveland, D.W., 1999. Slowing of axonal transport is a very early event in the toxicity of ALS-linked SOD1 mutants to motor neurons. Nat. Neurosci. 2, 50–56.
Wittstock, M., Pohley, I., Walter, U., Grossmann, A., Benecke, R., Wolters, A., 2012. Interhemispheric inhibition in different phenotypes of progressive supranuclear palsy. J. Neural Transm. 120, 453–461.
Wolters, A., Classen, J., Kunesch, E., Großmann, A., Benecke, R., 2004. Measurements of transcallosally mediated cortical inhibition for differentiating parkinsonian syndromes. Mov. Disord. 19, 518–528.
Yabe, I., Tsuji-Akimoto, S., Shiga, T., Hamada, S., Hirata, K., Otsuki, M., et al., 2012. Writing errors in ALS related to loss of neuronal integrity in the anterior cingulate gyrus. J. Neurol. Sci. 315, 55–59. https://doi.org/10.1016/j.jns.2011.11.039.
Yarnall, A.J., Rochester, L., Baker, M.R., David, R., Khoo, T.K., Duncan, G.W., et al., 2013. Short latency afferent inhibition: a biomarker for mild cognitive impairment in Parkinson's disease? Mov. Disord. 28, 1285–1288.
Yildiz, F.G., Saka, E., Elibol, B., Temucin, C.M., 2018. Modulation of cerebellar-cortical connections in multiple system atrophy type C by cerebellar repetitive transcranial magnetic stimulation. Neuromodulation 21, 402–408. https://doi.org/10.1111/ner.12589.
Zanette, G., Tamburin, S., Manganotti, P., Refatti, N., Forgione, A., Rizzuto, N., 2002. Different mechanisms contribute to motor cortex hyperexcitability in amyotrophic lateral sclerosis. Clin. Neurophysiol. 113, 1688–1697.
Zhang, J., Lu, H., Zhu, L., Ren, H., Dang, G., Su, X., et al., 2021. Classification of cognitive impairment and healthy controls based on transcranial magnetic stimulation evoked potentials. Front. Aging Neurosci. 13. https://doi.org/10.3389/fnagi.2021.804384.
Zhang, W., Zhang, L., Liang, B., Schroeder, D., Zhang, Z.-W., Cox, G.A., et al., 2016a. Hyperactive somatostatin interneurons contribute to excitotoxicity in neurodegenerative disorders. Nat. Neurosci. 19, 557–559. https://doi.org/10.1038/nn.4257.
Zhang, Y.-J., Gendron, T.F., Grima, J.C., Sasaguri, H., Jansen-West, K., Xu, Y.-F., et al., 2016b. C9ORF72 poly(GA) aggregates sequester and impair HR23 and nucleocytoplasmic transport proteins. Nat. Neurosci. 19, 668–677.
Zhu, L., Cai, M., Pei, Z., Shi, X., Dang, G., Lan, X., et al., 2025. Concurrent TMS-EEG to characterize cortical responses in the motor and prefrontal cortices in Parkinson's disease. Neurotherapeutics. https://doi.org/10.1016/j.neurot.2025.e00577.
Ziemann U. Pharmaco-transcranial magnetic stimulation studies of motor excitability, 2013, p. 387–97. 10.1016/B978-0-444-53497-2.00032-2.
Ziemann, U., 2004. TMS and drugs. Clin. Neurophysiol. 115, 1717–1729. https://doi.org/10.1016/j.clinph.2004.03.006.
Ziemann, U., Reis, J., Schwenkreis, P., Rosanova, M., Strafella, A., Badawy, R., et al., 2015. TMS and drugs revisited 2014. Clin. Neurophysiol. 126, 1847–1868. https://doi.org/10.1016/j.clinph.2014.08.028.
Ziemann, U., Siebner, H.R., 2015. Inter-subject and intersession variability of plasticity induction by non-invasive brain stimulation: Boon or bane? Brain Stimul. 8, 662–663. https://doi.org/10.1016/j.brs.2015.01.409.
Ziemann, U., Tergau, F., Wassermann, E.M., Wischer, S., Hildebrandt, J., Paulus, W., 1998. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J. Physiol. 511, 181–190.
Ziemann, U., Winter, M., Reimers, C.D., Reimers, K., Tergau, F., Paulus, W., 1997. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis - evidence from paired transcranial magnetic stimulation. Neurology 49, 1292–1298.
Zifman, N., Levy-Lamdan, O., Hiller, T., Thaler, A., Dolev, I., Mirelman, A., et al., 2024. TMS-evoked potentials unveil occipital network involvement in patients diagnosed with Parkinson's disease within 5 years of inclusion. NPJ Parkinsons Dis 10. https://doi.org/10.1038/s41531-024-00793-0.