

Review

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Review

Neurophysiologic Innovations in ALS: Enhancing Diagnosis, Monitoring, and Treatment Evaluation

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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive disease of both upper motor neurons (UMNs) and lower motor neurons (LMNs) leading invariably to a decline in motor function. The clinical exam is foundational to the diagnosis of the disease and ordinal severity scales are used to track its progression. However, the lack of objective biomarkers of disease classification and progression delay clinical trial enrollment and muddle inclusion criteria. Ultimately, biomarker evidence of therapeutic target engagement will support and perhaps supplant more traditional clinical trial outcome measures. Electrophysiology tools of nerve conduction study and electromyography have already been established as diagnostic biomarkers of LMN degeneration in ALS, with the more recent introduction of motor unit number estimation (including MScanFit), motor unit number index, and electrical impedance myography. Dysfunction of UMN and non-motor brain areas is being increasingly assessed with transcranial magnetic stimulation, high-density electroencephalography, and magnetoencephalography. Although most of these techniques are used to explore the underlying disease mechanisms of ALS in research settings primarily, they have the potential on a broader scale to noninvasively identify disease subtypes, predict progression rates, and assess physiologic engagement of experimental therapies.

Keywords: Amyotrophic lateral sclerosis (ALS); Motor unit number estimation (MUNE); Transcranial magnetic stimulation (TMS); Biomarker, Clinical trial

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common adult motor neuron disease (MND), which is characterized by the relentless loss in varying proportions of both upper motor neurons (UMNs) in the brain and lower motor neurons (LMNs) in the brainstem and spinal cord. Although the crude worldwide incidence and prevalence of ALS is estimated at 1.59 per 100,000 person-years and 4.42 per 100,000 population [1], significant regional variations have been reported [2–5].

Understanding disease presentation and characteristics has evolved from purely a clinical diagnosis to one currently supported by electrodiagnostic criteria, although still heavily reliant on the neurologic examination. Current ALS diagnostic criteria include the revised El Escorial Criteria [6,7] supplemented by the Awaji electrodiagnostic modifications [8] as well as the Gold Coast Criteria [9]. These criteria have been well described in the literature and rely upon demonstrating progressive motor neuron dysfunction with varying degrees of diagnostic certainty. However, these diagnostic criteria are complex to apply, and patients often experience significant delays in diagnosis, which may bias MND clinical trials with patients presenting in later stages of disease.

Paralleling the development of categorical diagnostic criteria, functional markers of disease progression have been devised, with attention to patient-reported symptom burden via the revised ALS-Functional Rating Scale (ALSFRS-R) [10], muscle strength by MRC sum score or hand-held dynamometry, and respiratory function by vital capacity measures [11]. Developing neurophysiologic biomarkers revealing early disease progression or engagement of pathophysiologic

targets would assist patient stratification in clinical trials and ultimately generate new trial outcome measures, fulfilling critical needs in the MND field.

From its conception in the 1970's, the goal of employing electrodiagnostic techniques to explore the integrity of functional motor units has remained an area of focus in the MND field. Because of degeneration of LMNs and their subsequent incomplete reinnervation, ALS and LMN-predominant MNDs (e.g. progressive muscular atrophy, Kennedy disease) are ideal conditions to use motor-unit number estimation (MUNE) and other electrodiagnostic techniques to describe the complex progressive LMN pathology. Furthermore, neurophysiologic assessment of UMN dysfunction is important for objective characterization of ALS and UMN-predominant MNDs (e.g. primary lateral sclerosis), as current diagnostic paradigms rely almost solely on bedside examination.

2. Lower Motor Neuron Assessment

2.1. MUNE History

In neuromuscular medicine, the assessment of a single motor unit and its recruitment pattern requires significant training, mastery of technique, appropriate participation by the patient, and a sense of the rater's own self-reliability. In the 1970's, electrodiagnostic research groups sought to achieve more objective assessments of the motor unit. McComas et al. derived the first motor-unit number estimation (MUNE) technique in which incremental sub-threshold stimulation of a single nerve-muscle pair was used to generate a stimulus-response curve, with the graded increase of compound muscle action potential (CMAP) response averaged to approximate the single-motor unit action-potential (SMUP) amplitude. That SMUP amplitude was divided into the supra-threshold generated CMAP of the same nerve-muscle pair, with the resultant value approximating the number of motor units [12].

The advent of a novel MUNE technique was not without criticism, and later groups challenged the assumptions of the McComas method, most critically that the earliest recruited SMUP's have distinct firing levels and that they are representative of the population of later recruited SMUP population in that same muscle [13]. Given the concern that there could be significant alternation of SMUP firing in the earliest recruited motor units, a multi-point stimulation motor unit estimation method was devised to better characterize the population of early motor unit recruitment [13,14]. Multi-point stimulation remains a tool to which more recently developed MUNE techniques are compared (MUNIX, MScanFit as described later in the text), and demonstrates strong reproducibility and ability to differentiate MND patients from health controls [15].

2.2. Motor Unit Number Index

The motor unit number index (MUNIX) technique describes an idealized motor unit number estimation from the parameters of the maximal compound muscle action potential (CMAP) of a given muscle and a surface-EMG interference pattern (SIP) across multiple levels of isometric force provided by the patient, yielding an ideal case motor unit count (ICMUC) [16]. The ICMUC is defined by $[CMAP\ Power * SIP\ Area] / [CMAP\ Area * SIP\ Power]$ which approximates the number of motor units for a given muscle. A further term, the motor unit size index (MUSIX) is derived from the CMAP amplitude divided by the MUNIX. In healthy controls across multiple assessed muscles, ranges of normative values have been tabulated and MUNIX has correlated well to CMAP amplitude [17,18]. The clinical application of MUNIX has proven to be reproducible in test-retest models with strong inter- and intra-rater reliability [18].

2.3. MUNIX as a Diagnostic/Categorical Biomarker

MUNIX values of ALS patients are significantly lower than those of healthy controls with motor unit loss by MUNIX detected in ALS patients well before a decline in CMAP amplitude can be identified by traditional nerve conduction study (NCS)[19]. MUNIX loss has reliably demonstrated a steeper decline than currently used physiologic markers of MND severity and progression, including the revised ALS-functional rating scale (ALSFRS-R) and slow vital capacity (SVC)[10,19] (**Figure 1**)

prompting investigators to consider whether MUNIX-based motor unit estimation could serve as an electrodiagnostic biomarker in ALS at multiple phases of clinical trial design. More recently, MUNIX mean scores have been shown to significantly predict more rapid rates of ALS disease progression measured by serial ALSFRS-R responses [20]. Other groups have attempted to enrich the sensitivity and specificity of MUNIX-based testing by incorporating known clinical phenomena seen in ALS, namely the presence of the split-hand pattern, in which CMAP amplitudes are lower in the abductor pollicis brevis (APB) and/or first dorsal interosseous (FDI) muscles than in the relatively spared abductor digiti minimi (ADM) muscle [21,22]. The split-hand MUNIX, $[(\text{APB MUNIX} * \text{FDI MUNIX}) / \text{ADM MUNIX}]$, has been shown to better differentiate ALS patients from healthy controls than a previously described CMAP-based split hand index and better correlate with the ALSFRS-R [23]. MUNIX decline has therefore been considered a potential biomarker of disease severity at inclusion to a clinical trial, an early sign of disease progression once enrolled in a trial, and ultimately a stabilization in the decline of MUNIX as a hopeful sign of pharmacodynamic target engagement as a trial outcome[24].

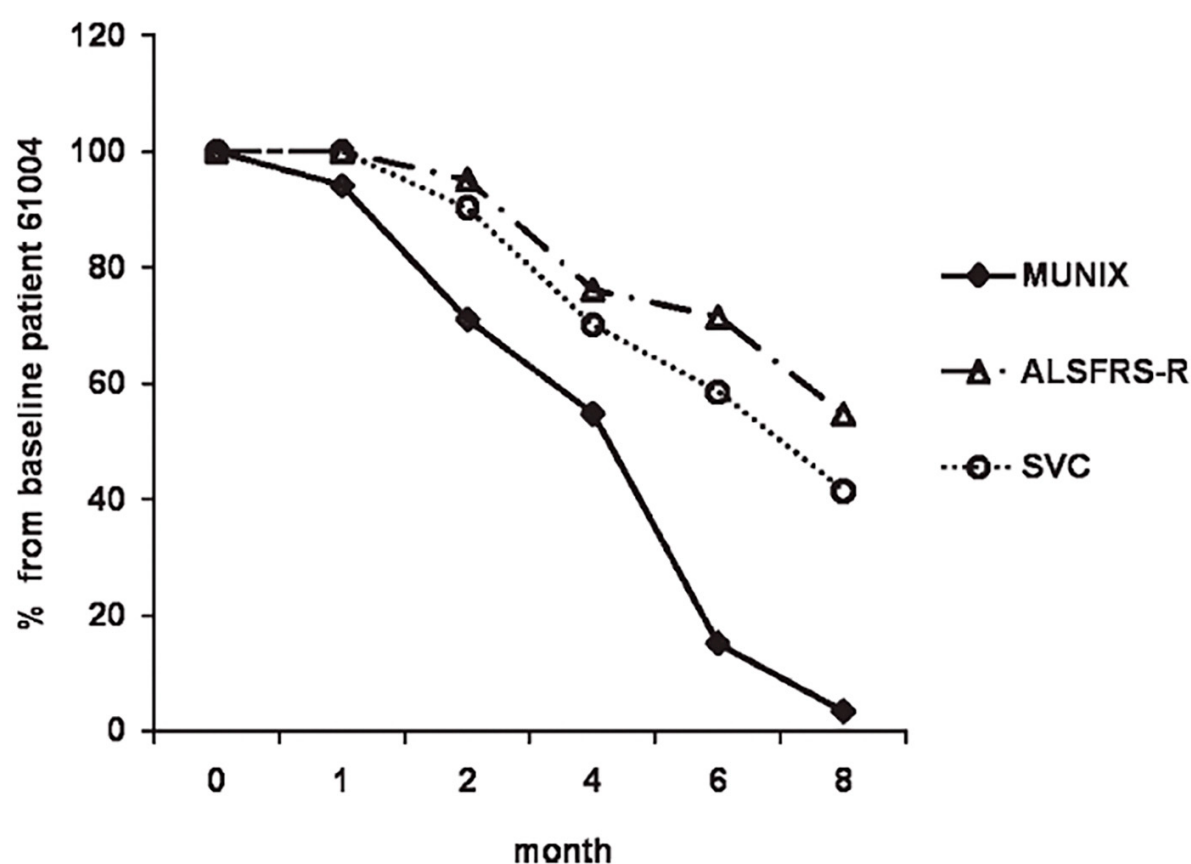


Figure 1. Relative percent drop of the motor unit number index (MUNIX) in a patient with ALS is greater and detected earlier than changes in the revised ALS functional rating scale (ALSFRS-R) score and slow vital capacity (SVC). (Modified and used with permission from reference #19).

2.4. MUNIX as a Marker of Disease Progression/Pharmacodynamic Biomarker

Beyond its use as an adjunct in ALS diagnosis and disease-severity stratification, MUNIX has also been utilized in the assessment of disease progression. Decline in MUNIX of single muscles as well as the sum of multiple MUNIX values has correlated well with previously established markers of ALS disease progression, namely the ALSFRS-R [25,26]. In some studies, the relative rate of progressive decline in MUNIX values was greater than that of the ALSFRS-R and could even precede the development of clinical objective weakness evaluated by manual muscle testing [27]. Given the apparent early clinical changes in ALS by MUNIX compared with more traditional assessments of

motor function, there has been interest in employing this technique as a pharmacodynamic biomarker in ALS clinical trials. Studies have estimated that employment of MUNIX as a defined clinical outcome in trials could reduce both the time needed to assess therapeutic efficacy and reduce the number of participants required to generate statistical significance. The RESCUE ALS investigators used the mean percent change in summed MUNIX score as the primary outcome in their CNM-Au8 gold nanoparticle antioxidant trial in ALS, which, while not demonstrating significant change in MUNIX values between the trial arms, did show that this technique could prove useful in future clinical studies[28,29]. There are many active and recently closed clinical trials employing MUNIX as a secondary outcome with the goal that reduction of MUNIX decline could prove a useful electrodiagnostic biomarker of target engagement [30–32].

The use of MUNIX in the clinical assessment of ALS patients has not been without criticism. One of the most common critiques of the MUNIX technique is that it requires the participation of the patient to provide varying levels of force to generate different surface interference patterns on surface EMG, thus making the technique difficult to apply to patients with comorbid cognitive impairment and in non-functional muscle [33]. There is also some concern from other groups that MUNIX may not obtain a fully representative sample of motor units[34]. Nonetheless, given the shorter acquisition time and robust data supporting its use, MUNIX remains a widely applied technique in the MND clinical trial landscape.

2.5. MScanFit

Given the questions raised above about MUNIX and its limitations, newer models of motor unit investigation have been designed, with the MScanFit MUNE technique emerging as another prospective electrodiagnostic ALS biomarker. Unlike MUNIX, MScanFit fits a mathematical model to a graded CMAP stimulus-response curve, which presumes to consider the variability of all the motor units recorded over a given muscle and generate a motor unit number estimation [34]. Jacobsen et al. demonstrated that MScanFit reliably differentiated ALS patients from healthy controls better than MUNIX, at the cost of a longer examination time [34]. Furthermore, MScanFit demonstrated larger rates of decline per month in ALS patients compared with alternate MUNE techniques, as well as with traditional markers of ALS disease progression including worsening ALSFRS-R scores and CMAP amplitude decline [35]. Adding the characterization of the split-hand index to MScanFit exhibited greater diagnostic sensitivity and specificity than competing split-hand MUNE techniques [36]. MScanFit has also been used to shed light on the putative mechanisms of ALS disease pathophysiology, demonstrating that the pattern of neurodegeneration in the distal muscles precedes that of proximal muscles, suggesting a dying-back phenomenon occurring at the level of the lower motor neuron [33]. The clinical trial landscape has begun to employ MScanFit into trial design, with the recently closed trial RESCUE ALS trial and the active trial RANTAL (NCT06219759) trial using the technique.

2.6. The Neurophysiologic Index and F-Wave Investigations

In parallel to the development of motor unit number estimation techniques, other groups have investigated more traditional electrodiagnostic parameters, with efforts focused on incorporating the F-wave characteristics into MND biomarkers. The neurophysiologic index was developed based on observations that declining CMAP amplitude, prolonging distal motor latency, and decreasing frequency of F-wave responses correlated with loss of muscle bulk and clinical weakness, ultimately described by the formula $NPI = [CMAP \text{ amplitude} / \text{Distal Motor Latency}] \times (\text{F-wave frequency over 20 recordings})$ [37]. This index has proven to be well-correlated with muscle strength and is a more sensitive indicator of clinical decline than more traditional MND biomarkers like FVC and delta-ALSFRS-R [38,39]. Attention to other parameters of the F-wave, including the assessment of identical “repeater F-waves” have demonstrated differentiation of ALS patients from healthy controls depending on the muscle assessed. This is thought to be possibly related to the split-hand phenomenon when comparing the ADM and APB CMAPs and has generated an additional MUNE method from the F-wave data [40,41].

2.7. LMN Hyper-Excitability

Another characteristic of MND pathophysiology is the concomitant axonal hyperexcitability that generates fasciculation potentials. Many properties of axonal hyperexcitability have been explored, most notably the strength-duration time constant (SDTC) reflecting Na⁺ current permissibility and threshold electrotonus (TE) representing axonal membrane accommodation due to K⁺ currents [42]. First described by Bostock and colleagues in 1995, the principle of threshold electrotonus is to evoke a submaximal CMAP at different initial stimulus intensities and add a second polarizing current pulse, which provides a threshold response-time curve reflecting accommodation of the nerve to the polarized current [43]. In this study, ALS patients showed two populations of TE responses in contrast to both healthy and other-neurologic-condition controls – a greater threshold reduction than control suggesting hyper-excitability (deemed type I responders) or a rapid increase in threshold representing significant hyperpolarization (type II responders); both pathophysiologies are thought to reflect abnormal K⁺ channel conductance [42,43]. The strength-duration time constant (SDTC) describes the rate of stimulus current decline as duration of a threshold stimulation increases, which is dependent partially on Na⁺ channel conductance [42]. Interestingly, the SDTC is increased in ALS patients compared with healthy controls, distinguishing those two groups even in early disease states when CMAP's are in the normal range [44]. Thus, the identification of electrophysiologic markers of axonal hyperexcitability has both garnered interest in its use as a clinical trial biomarker and as a therapeutic target in MND, given the hypothesized abnormal axonal ion channel conductance described.

2.8. Electrical Impedance Myography

While traditional NCS-based and MUNE tools have generated much interest in ALS research, a parallel investigation into the electrophysiologic properties of affected muscle has also garnered attention as a possible biomarker of MND. Electrical impedance myography (EIM) describes the electrophysiologic properties of a given muscle, namely the electrical resistance to low-intensity but high-frequency electrical current and the phase which is a measure of cell membrane integrity and its ability to alter the application of an alternating current [45]. This tool is non-invasive, quick to use, and relies on the inherent architecture of the underlying muscle. The phase parameter showed promising sensitivity (90%) and specificity (100%) in differentiating ALS patients from healthy controls [46]. Furthermore, the coefficient of variation of EIM when used to track the rate of decline in ALS out-performed that of hand-held dynamometry and the ALSFRS-R [47]. It has been proposed that EIM when used as a biomarker of therapeutic target engagement could significantly reduce the number of patients required in future clinical trials when compared with the traditionally used ALSFRS-R [47,48]. Another highlight of the EIM technique is its ability to assess bulbar disease progression, which is more difficult to characterize by traditional clinical measures (i.e. bulbar sub-score of the ALSFRS-R, vital capacity measurements). EIM of the tongues of ALS patients demonstrates reduced phase and increased resistance compared with those of healthy controls [49]. With the advent of improved computational processing, a new technique called Tensor-EIM characterizes a multi-directional assessment of tongue muscle electrical impedance [50]. This tool was projected in a hypothetical clinical trial scenario to reduce the number of needed participants significantly compared with the ALSFRS-R bulbar sub-score in an ALS patient cohort [50].

3. Upper Motor Neuron Assessment

3.1. Transcranial Magnetic Stimulation (Single-Pulse and Paired-Pulse Models)

Though understanding of LMN dysfunction in ALS has been well characterized by traditional and research electrodiagnostic methods, the characteristics of upper motor neuron (UMN) pathophysiology remain challenging. At the time of this report, there is still no electrophysiologic tool to detect UMN dysfunction in routine clinical practice. Transcranial magnetic stimulation (TMS) is a noninvasive method for understanding the pathophysiology of UMN dysfunction by using a

targeted magnetic pulse to induce a stimulating electric current within the primary motor cortex. This in turn activates the corticomotoneuron pool and generates a motor evoked potential (MEP) in the relevant contralateral muscle [51,52] (**Figure 2**)[53].

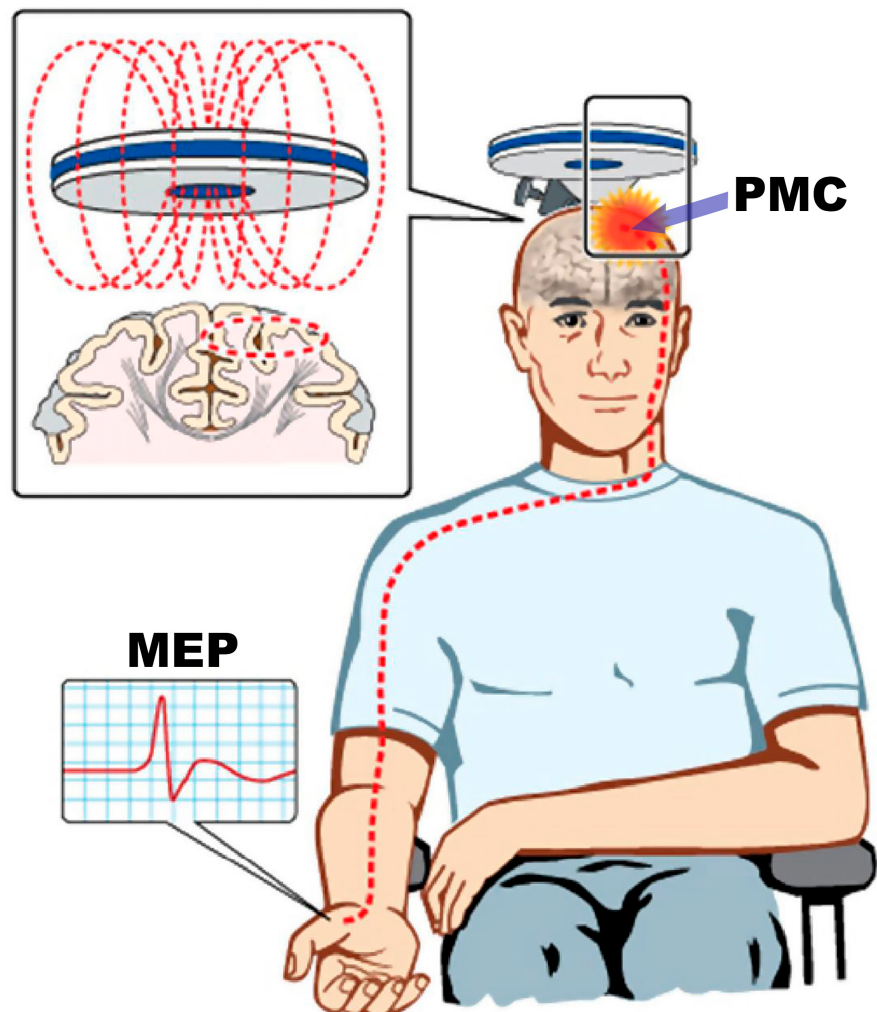


Figure 2. Transcranial magnetic stimulation excites a network of neurons in the underlying primary motor cortex (PMC) with a motor evoked potential (MEP) recorded over a contralateral intrinsic hand muscle (abductor pollicis brevis). (Modified and used with permission from reference #53).

Within the TMS literature, both single-pulse and multi-pulse paradigms have been used with success in differentiating ALS disease characteristics from controls. Single pulse TMS methods have demonstrated that patients with ALS have increased motor evoked potential (MEP) amplitudes and a steeper MEP response-curve when compared to healthy controls [54] or disease mimics [55]. Additional studies highlight that the cortical silent period, which is the duration of electromyographic silence following a TMS stimulus, is reduced significantly in ALS compared with both healthy controls and ALS disease mimics [56]. Further work in paired-pulse TMS models by Vucic and colleagues, in which subthreshold conditioning stimuli are delivered at different interstimulus time intervals and the effect of that preconditioning stimulus on the amplitude of a second applied stimulus needed to generate a fixed MEP amplitude (called threshold-tracking TMS) is assessed, has further explored the underpinnings of UMN dysfunction in MND [57].

Two promising threshold-tracking paired-pulse TMS parameters differentiating ALS from controls are short-interval cortical-inhibition (SICI) and intracortical facilitation (ICF). SICI which is described by the increase in the conditioned stimulus intensity needed to maintain a targeted MEP, is significantly reduced in ALS patients from control subjects, most prominently in patients with spinal-onset ALS [57]. This reduced SICI period in ALS patients is followed by a period of increased

ICF, which is manifested by a decrease in the stimulus intensity required to maintain the target MEP amplitude. These findings suggest underlying corticomotoneuronal signaling hyperexcitability [57]. This has been validated by multiple groups in recent years, and that increased cortical hyperexcitability is correlated with shorter survival [58,59] as well as with ALS-associated cognitive impairment [60]. Furthermore, Otani and colleagues combined the measures of elevated SDTC reflecting LMN hyperexcitability with reduction in SICI into a prognostic model showing ALS patients manifesting both central and peripheral hyperexcitability have significantly reduced survival compared to ALS patients with one or no hyperactive parameters[59].

Additional work by Vucic and colleagues in symptomatic familial ALS (fALS) patients carrying the superoxide dismutase type 1 (SOD1) mutation revealed similar reduction in SICI and increased ICF in this specific cohort; asymptomatic SOD1 fALS patients also demonstrated significant reduction in SICI prior to development of clinical symptoms[61]. This finding suggests that cortical hyperexcitability may precede clinical symptoms of ALS, which are manifestations of predominantly LMN death, the putative “dying forward hypothesis” [61]. This technique has further evaluated the therapeutic effects of riluzole in significantly increasing SICI in patients with ALS treated with riluzole compared to untreated ones [62]. Ultimately, this foundational work suggests that (a) corticomotoneuronal hyperexcitability may precede the clinical syndrome of ALS and differentiate such patients from controls, (b) this hyperexcitability can be modulated by approved ALS therapies, and (c) use of such techniques as a categorical and pharmacodynamic biomarkers in future clinical trials is warranted [52,63].

3.2. *Peristimulus Time Histograms in ALS Patients*

In addition to studying the MEP after applying TMS over a region of motor cortex, investigations led by Eisen and colleagues used the peristimulus time histogram (PSTH) technique to characterize the probability of firing a single voluntarily-activated motor unit after a single motor cortex directed impulse. This approach allows for the investigation of a small pool of TMS-activated corticomotoneurons and their converging excitatory post-synaptic potentials on the spinal motor neuron, which leads to changes in the firing probability of the respective motor unit [64]. Normally, when a voluntarily recruited single motor unit encounters a TMS-induced corticomotoneuron volley, an increased probability of motor unit firing occurs with a latency of 20 milliseconds after the stimulation; this is the primary peak, which reflects the compound excitatory post-synaptic potential (EPSP) [65]. In normal aging, there is a linear decline of the EPSP amplitude, while in purely lower motor neuron disorders there is no change to the EPSP [65]. In ALS, multiple PSTH patterns have been demonstrated, likely reflecting differing time-points across disease progression. While most ALS patients exhibit a reduced or absent EPSP, another subset demonstrates higher than expected EPSP amplitudes for age [65]. Later studies demonstrated a delay in the primary peak onset, increased temporal dispersion and more EPSP peak sub-components in the post-TMS corticomotoneuron volley period within ALS subjects [66,67]. These changes are theorized to reflect asynchronous temporal summation of the descending corticomotoneuron volley as well as increased repetitive firing of a hyperactive corticomotoneuronal pool in ALS [67]. This method provides an additional way to study progression of UMN degeneration in ALS, and possibly serve as a pharmacodynamic biomarker of therapeutic target engagement in clinical trials.

3.3. *High Density EEG and MEG*

Given the known association of ALS with frontotemporal dementia, as well as the growing understanding of non-motor manifestations of ALS, it is important to assess the function of distributed brain networks in this condition. Resting state high density EEG (HDEEG) demonstrates increased connectivity across the fronto-central cerebrum of cognitively normal ALS patients thought to reflect pathologic hyperconnectivity within the Salience and Default Mode networks [68]. Further studies into event-related potentials (ERPs) show that there are significant differences in mismatch negativity (an ERP reflecting the late potential difference between expected and deviant auditory

tones) as well as in the sustained attention to response task network delineating ALS patients from healthy controls [69,70]

Magnetoencephalography (MEG) has also been useful in MND electrophysiology, as high-definition resolution of cortical beta band synchronization helps illuminate the role of this synchronization in movement preparation and execution, as well as the dysfunction of this local network in ALS [71]. ALS patients demonstrate augmented beta band desynchronization in the bilateral motor cortex during movement preparation phase, followed by a delayed rebound of beta power after movement completion which is thought to reflect local cortical hyperexcitability [71]. Like studies with EEG, resting-state MEG in ALS patients reveals diffusely increased connectivity throughout cortical networks, particularly within posterior cingulate cortex and its connections to the motor cortex [72]. These tools can reliably differentiate ALS patients from healthy controls, sub-stratify disease subtypes based exclusively on unique cortical network abnormalities, and possibly serve as both categorical and pharmacodynamic biomarkers of ALS cortical dysfunction in clinical trials [73].

4. Conclusion

ALS and related MNDs remain areas of intense research aimed at unraveling their complex pathophysiologies and developing effective therapies. The advancements in electrophysiologic techniques, including MUNE, MUNIX, MScanFit, EIM and TMS, have significantly enhanced our understanding of both UMN and LMN dysfunction. These methods offer promise not only in improving diagnostic accuracy and stratification but also in serving as sensitive biomarkers of disease progression and therapeutic target engagement. Furthermore, techniques like high-density EEG and MEG provide additional dimensions in tracking brain disease progression and even assessing non-motor manifestations of ALS. The integration of these advanced neurophysiologic tools into clinical trials has the potential to streamline the evaluation of therapeutic efficacy, ultimately accelerating the development of effective treatments for ALS and other MNDs. Continued research in this field is essential to refine these techniques and validate their clinical utility, bringing us closer to improving patient outcomes and quality of life.

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