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Review

Motor unit number estimation (MUNE): Where are we now?

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HIGHLIGHTS

- Methods to estimate the number of motor unit numbers are important in neurophysiology.
- Many methods have been developed, all with specific limitations.
- To understand the science behind MUNE is fundamental for its application.

ABSTRACT

Estimation of the number of motor units (MUNE) in specific muscles is important to monitor outcome in progressive neurogenic disorders, with potential application in clinical trials. However, in spite of recent developments to identify the most convenient technique for MUNE, all current methods have individual shortcomings. It is essential to understand the scientific concepts that support MUNE and the many methods already proposed. In particular, the core role of the compound muscle action potential (CMAP) size in the estimation process is undervalued. Operator-dependent variation in CMAP amplitude or area is the main factor underlying MUNE stability. At present, MUNIX, as standardized in many centers, is probably the best accepted method. Future developments should be based on full understanding of the neurophysiological concepts underlying the MUNE calculation, in order to find a quick, well-tolerated, operator-friendly and reliable method to apply more universally in clinical practice.

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Abbreviations: ALS, amyotrophic lateral sclerosis; CMAP, compound muscle action potential; CNEMG, concentric needle EMG; E1, preferred term for "active electrode"; E2, preferred term for "reference electrode"; MPS-MUNE, multi-point-motor unit number estimation; MU, motor unit; MUNE, motor unit number estimation; MUNIX, motor unit number index; Scanning CMAP, group of techniques including CMAP Scan, MScanFit, D50; SIP, surface interference pattern; SMA, spinal muscular atrophy; SMUP, surface-recorded motor unit potential.

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1. Introduction

Counting the number of motor units (MUs) in a muscle appears a deceptively simple task. Count the number of muscle fibers and count the number of motor axons supplying the muscle, then divide the former by the latter. But there's a problem. This erroneously assumes that each MU is approximately the same size. However, the innervation ratio varies between muscles (Feinstein et al., 1955). Also, type II MUs are larger than type I MUs and the proportions of these two basic MU types varies between muscles (Brooke and Engel, 1969; McComas et al., 1971). There are minimal anatomical data to use as a standard of reference, investigators have turned to clinical neurophysiological methods. Here the semantics are changed. One is not *counting* the number of MUs in a muscle but, rather, *estimating* them. And by the term estimation we mean not an estimate of number of motor units in the whole of the muscle, but rather an estimate in that portion of the muscle within the uptake area of the surface electrode. While the difference in terminology is clear, investigators should be careful to avoid becoming victims of definition when trying to interpret results or when comparing different techniques for Motor Unit Number Estimation (MUNE).

MUNE as an electrophysiological technique began with the seminal studies of manual incremented stimulation by McComas et al. (1971). Briefly:

> *The idea came to me when I was a subject for an experiment at Johns Hopkins during a summer vacation from the UK in 1968. The investigators having departed for lunch, I thought I would see if a single motor unit potential could be detected with a surface electrode over the hypothenar muscles, using liminal stimuli to the ulnar nerve. Once this was seen to be possible, the next step was obvious--to give a maximal stimulus and to compare the M-wave with the MU potential, thereby getting a number for the MU population. But I only took the matter up again after returning to the UK* (McComas, AJ: personal communication to PEB)

Alan McComas missed lunch that day.

The principle of MUNE is quite simple. Record the compound muscle action potential (CMAP) and measure its amplitude. This is the sum of surface recorded single motor unit potentials (SMUPs) of all MUs in the muscle. Next, record SMUPs from different MUs and calculate the average SMUP amplitude. Dividing this in to the CMAP gives MUNE.

$$\text{MUNE} = \text{CMAP amplitude}/\text{average SMUP amplitude}$$

One could also potentially use area instead of amplitude.

McComas and colleagues described the so-called incremental stimulation method. The CMAP was recorded using standard nerve conduction techniques (Fig. 1A, top trace). Next, the nerve was stimulated by increasing the intensity in very fine steps. With stimulation of each additional axon, the response changed in a step-wise manner (Fig. 1A, bottom traces). The amplitude of the largest response was divided by the number of steps, i.e. number of stimulated axons, to estimate the average amplitude of an SMUP. Dividing this in to the CMAP amplitude gave an estimate for the number of MUs.

MUNE did not gain much atraction until the late 1970s, when the multiple point ("multi-point") stimulation (MPS MUNE) technique was introduced. This method was designed to overcome the problem of alternation, recognized as a potential limitation in the original method described by McComas et al. (1971). Alternation may occur when two or more MUs have a similar threshold and their individual responsiveness to the same stimulus intensity varies (Brown and Milner-Brown, 1976; Kadrie et al., 1976). In this multi-point stimulation technique, single SMUPs are obtained by stimulating the nerve at different points, at threshold intensity. At least 10, often 15–20 SMUPs are used to derive a mean SMUP amplitude. Because this method is time-consuming a modification was proposed (Adapted MPS-MUNE) by combining the classical incremental technique and multiple point stimulation (using 4–6 different sites).

Several additional variations in MUNE methodology were proposed over the years (Doherty and Brown, 1993; Wang and Delwaide, 1995). The method used by Shefner et al. (2011) is illustrated in Fig. 1B. The CMAP is recorded using standard motor nerve conduction methods. Next, incremental stimulation is used to record from 3 MUs from each of three different stimulation sites. The average amplitude from the 9 MUs is used for MUNE. In the 1980s interest in MUNE was reinforced by the introduction of a new technique, the spike-triggered averaging technique, which is feasible in proximal muscles, e.g., biceps brachii (Nandedkar and Barkhaus, 1987; Brown et al., 1988; Strong et al., 1988), as well as in distal muscles, like as hand muscles (Van Asseldonk et al., 2006). This renewed interest was in part driven by technical developments and digitization in electromyograph systems. A needle electrode was inserted in the tested muscle to record sharp EMG signals. An amplitude trigger was used on the needle recordings to time lock and average the signals from a single MU using the surface electrode. Averaged amplitude from several MUs was the divisor against the CMAP amplitude for MUNE (Fig. 1C).

Other techniques followed including Automated Incremental Stimulation (Galea et al., 2001), F Response Method (Stashuk et al., 1994), Statistical Method (Daube, 1995), MUNIX (Nandedkar et al., 2004, 2010; Neuwirth et al., 2011), use of Bayesian statistics (Ridall et al., 2006), applying High Density Surface EMG (HDSEMG) (van Dijk et al., 2008) and CMAP Scanning (Visser and Blok, 2009; Bostock, 2016; Jacobsen et al., 2017). Recent methods have approached the problem of SMUP amplitude in a different way. Rather than identifying and recording individual MUs, statistical and mathematical models are used to study signal from several MUs, during stimulation or voluntary activation. This allows one to automate and standardize the method. It may also save time. The statistical method described by Daube (1995) was available commercially and widely tested. It used a Poisson distribution to model the variability of signal amplitude at submaximal stimulation, and to assess the SMUP amplitude. However, since variability also results from abnormal neuromuscular transmission during reinnervation, this method fell out of favor.

HDSEMG recordings can be used to extract SMUPs for MUNE studies following incremental or multiple-point stimulation by using different decomposition algorithms (van Dijk et al., 2008), this technique showed good reproducibility and sensitivity to