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Brief Communication

Motor Unit Number Index of the Upper Trapezius: A Meta-Analysis and Cross-sectional Study of Its Reliability

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ABSTRACT: Motor unit number index of the upper trapezius (MUNIX-Trapezius) is a candidate biomarker for bulbar lower motor neuron function; however, reliability data is incomplete. To assess MUNIX-Trapezius reliability in controls, we conducted a systematic review, a cross-sectional study ($n = 20$), and a meta-analysis. We demonstrated a high inter- and intra-rater intraclass correlation (0.86 and 0.94, respectively), indicating that MUNIX-Trapezius is reliable with between-study variability moderated by age and MUNIX technique. With further validation, this measure can serve as a disease monitoring and response biomarker of bulbar function in the therapeutic development for amyotrophic lateral sclerosis.

RÉSUMÉ : Estimer le nombre d'unités motrices du faisceau supérieur du muscle trapèze : une méta-analyse et une étude transversale de la fiabilité de ce biomarqueur. L'indice du nombre d'unités motrices du faisceau supérieur du muscle trapèze (*motor unit number index of the upper trapezius*) est un biomarqueur candidat en ce qui regarde la fonction des motoneurones inférieurs de la région bulbaire. Cela dit, les données sur sa fiabilité demeurent incomplètes. Pour l'évaluer chez des témoins, nous avons réalisé une revue systématique, une étude transversale ($n = 20$) ainsi qu'une méta-analyse. Nous avons pu démontrer ainsi une forte corrélation intra-classe inter et intra-évaluateur (respectivement 0,86 et 0,94), ce qui indique que ce biomarqueur est fiable avec une variabilité inter-étude modérée par son utilisation et l'âge. Avec une validation plus poussée, l'indice du nombre d'unités motrices du faisceau supérieur du muscle trapèze peut permettre le suivi de la sclérose latérale amyotrophique (SLA) et de la réponse de la fonction bulbaire dans le développement thérapeutique destiné à cette maladie.

Keywords: Motor unit number index; Trapezius; Reliability; Reproducibility; Meta-analysis

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Introduction

Motor unit number index (MUNIX) is a neurophysiological technique that indirectly estimates the number of functioning motor units of a given muscle. Calculated by modeling the compound motor action potential (CMAP) and surface interference pattern (SIP),[1] MUNIX correlates with other motor unit number estimation (MUNE) methods with excellent reliability in limb muscles.[2] The technique can be employed as an outcome measure for multicentre clinical trials[3] and there are guidelines to assure consistent recording and analysis across laboratories.[4]

MUNIX is a candidate biomarker of longitudinal lower motor neuron (LMN) dysfunction and has been adopted in limb muscles of patients with amyotrophic lateral sclerosis (ALS) as an outcome of early-phase trials.[3] However, MUNIX of brainstem-innervated muscles remains technically challenging, which limits its application in monitoring LMN progression in bulbar-ALS. MUNIX of facial nerve-innervated muscles has been explored as a potential correlate for bulbar dysfunction, but there has been poor discrimination between scores from patients with bulbar weakness and controls.[5]

Given the limitations associated with longitudinal assessment of tongue and facial denervation, examination of the upper trapezius (UTrap) may be a more feasible surrogate measure of bulbar LMN dysfunction. Despite UTrap's motor neurons likely localizing in the cervical spine, UTrap neurogenic denervation was demonstrated by needle EMG in early ALS bulbar weakness.[6] In two small studies, MUNIX of the UTrap (MUNIX-Trapezius) had

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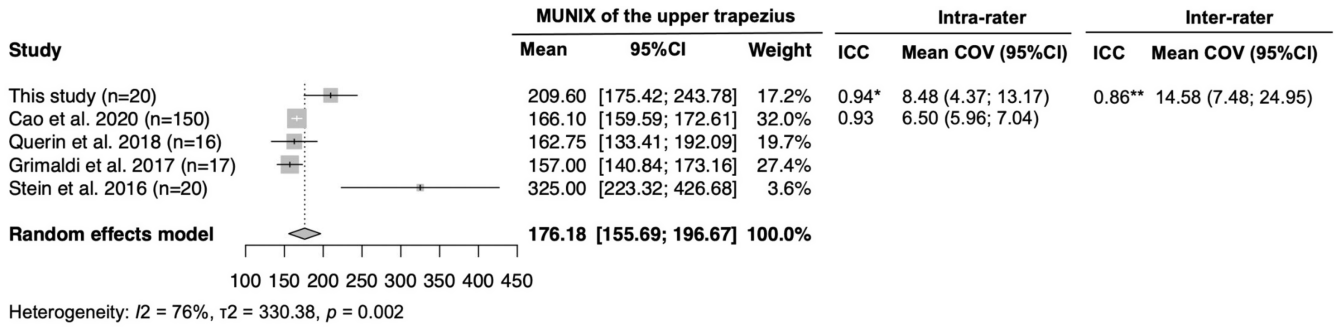

Figure 1: Forest plot of mean MUNIX of the upper trapezius in healthy volunteers from four published studies, in addition to data from this study. 95%CI of mean CoV for Cao et al. was estimated using the Mean ± (SD/$\sqrt{}$n × 1.96) from their published data. * $n = 20$; ** $n = 10$.

lower mean scores in ALS patients compared to controls.[5,7] Although adequate intra-rater reliability was recently reported in healthy volunteers,[8] there is no data on inter-rater reliability to further validate its utility in multicentre studies.

The objective of this study is to 1) conduct a systematic review of studies reporting MUNIX-Trapezius scores and reliability data in control participants; 2) perform MUNIX-Trapezius in control volunteers to assess inter- and intra-rater intraclass correlations (ICC); and 3) perform a meta-analysis of pooled MUNIX-Trapezius measurement parameters to determine the utility of this measure as a marker of bulbar dysfunction in future ALS studies.

For the systematic review, Medline and EMBASE were searched in April 2022 using the terms ("MUNIX" OR "motor unit number index") AND ("trapezius" OR "spinal accessory nerve" OR "accessory nerve") without language or date filters (Supplementary A.1). Inclusion criteria were original articles reporting MUNIX-Trapezius of control participants. Excluded were conference abstracts and non-peer-reviewed publications. Two independent reviewers screened and extracted data from eligible articles following the PRISMA 2020 guidelines.

For assessing reliability, we enrolled volunteers aged 18 years and older without a medical history or exposure to medications associated with a risk of neuropathy. The study was approved by the local ethics board and written informed consent was obtained from all volunteers. Participants were seated upright with the active electrode (E1) placed over the motor point of the UTrap (about mid-point from C7 to acromion). The E2 electrode was placed over the contralateral acromion to ensure an isoelectric recording and to avoid volume-conducted potentials from ipsilateral co-activated muscles. We stimulated the right spinal accessory nerve at the posterior site, making all the efforts to achieve supramaximal CMAP, including multiple changes in E1 positioning.[4] CMAP baseline-peak amplitudes were recorded and filtered (2–10,000 Hz). Twenty 500-ms SIP epochs were recorded and filtered (20–10,000 Hz) at five-increasing levels of voluntary shoulder shrug. All tests were performed on a Natus VikingQuest™ v22 system. Two or three unilateral MUNIX sessions were performed 30 minutes apart by two blinded raters with all electrodes and markings removed and cleared in-between tests. Two sessions were performed by a novice neurophysiology fellow (Rater 1) and one session by a board-certified neurophysiologist with prior MUNIX experience (Rater 2).

Mean MUNIX values, standard deviation (SD), and 95% confidence interval (95%CI) of the mean were reported. Inter- and intra-rater reproducibility was calculated using two-way random effects model with multiple raters intraclass correlation (ICC[2,k]). The coefficient of variability (CoV) was calculated as the SD over the mean with bootstrap 95%CI estimated (10,000 resamples with replacement). Rater 1 test-retest data were used to calculate intra-rater reproducibility, whereas Rater 1 test and Rater 2 test data were used for inter-rater reproducibility. Bland–Altman plots demonstrated inter- and intra-rater agreement. A minimum sample size of 10 participants with two raters' repeated measures provided 83% power to detect an inter-rater ICC of 0.85 and a null hypothesis ICC of 0.2 at two-sided alpha 0.05. A random-effects meta-analysis of single-group MUNIX means was estimated using the inverse variance method and DerSimonian-Laird τ^2 estimator. Analyses were computed using R (metafor package).

There were four published studies reporting MUNIX-Trapezius for a total of 203 control volunteers (Figure A.1). The pooled mean MUNIX-Trapezius was 176.2 (95%CI 155.7; 196.7) in a meta-analysis of all available data including our enrolled cohort (Figure 1). There was significant heterogeneity in mean MUNIX values (I^2 76%), along with variability in age and sampling technique across studies (Table 1). Mean age varied across studies (Figure A.2) and moderated mean MUNIX-Trapezius values in a meta-regression model (Figure 2).

In our study, 20 volunteers (10 females) with mean age of 33 years (SD 9, range 23–56) were enrolled. Mean MUNIX was 209.6 (SD 78) without a floor or ceiling effect, while mean CMAP baseline-to-peak amplitude was 9.5 mV (SD 2.6). Inter-rater ICC ($n = 10$) of 0.86 indicated adequate reliability between a novice and an experienced rater. Intra-rater reliability ($n = 20$) performed by Rater-1 revealed excellent agreement, similar to data reported by Cao et al.[8] (Figure 1). Conforming to the MUNIX guidelines, inter- and intra-rater CoVs were below 20% with excellent agreement among raters as indicated by the Bland–Altman plots (Figure 3).

MUNIX has been demonstrated as a reliable biomarker of LMN dysfunction in limbs of patients with ALS. As a marker of bulbar LMN dysfunction, MUNIX-Trapezius has emerged as a candidate biomarker and a more reliable alternative to facial muscles.[5,7,9] In our systematic review, mean MUNIX values were heterogeneous across studies in controls and reliability data for this measure were incomplete, which limits its interpretation and implementation as a marker of bulbar LMN dysfunction in multicentre ALS studies. In contrast, we found that well-trained examiners following a systematic testing approach demonstrated excellent inter- and intra-rater reliability of this parameter in control participants.

MUNIX is susceptible to variability in SIP sampling, particularly at low contraction levels.[2] This may partially account for

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Table 1: Demographics and qualitative summary of MUNIX techniques used among studies

Study	*n*	Mean age (SD)	Females (%)	Hardware	Software	Technique	E1 repositioning for supramaximal CMAP?	Location of E2	Total number of SIPs	SIP epoch length	Levels of muscle contraction
This study	20	33 (9)	50	Nicolet VikingQuest[a] system (Natus)	Synergy v22 (Natus)	MUNIX guidelines (2018)	Yes	Contralateral acromion	20	500 ms	5
Cao* et al. *2020	150	49 (17)	49	Nicolet EDx system (Natus)	Natus v22	MUNIX guidelines (2018)	Yes	Not reported	At least 20	500 ms	5
Querin* et al. *2018	16	40 (13)	38	Nicolet VikingQuest[a] system (Natus)	Natus v21	Original MUNIX (2004)	Not reported	Not reported	At least 10	500 ms	Not reported
Grimaldi* et al. *2017	17	63 (7)*	53	Keypoint system (Medtronic)	Excel file provided by Keypoint	Original MUNIX (2004)	Yes	Ipsilateral acromion	10	300 ms	5
Stein* et al. *2016	20	24 (3)*	65	Schwarzer topas system (Natus)	LabView Ver11 (National Instruments)	Continuous SIP	Yes	Not reported	50	Continuous	Not reported

*Estimated SD.

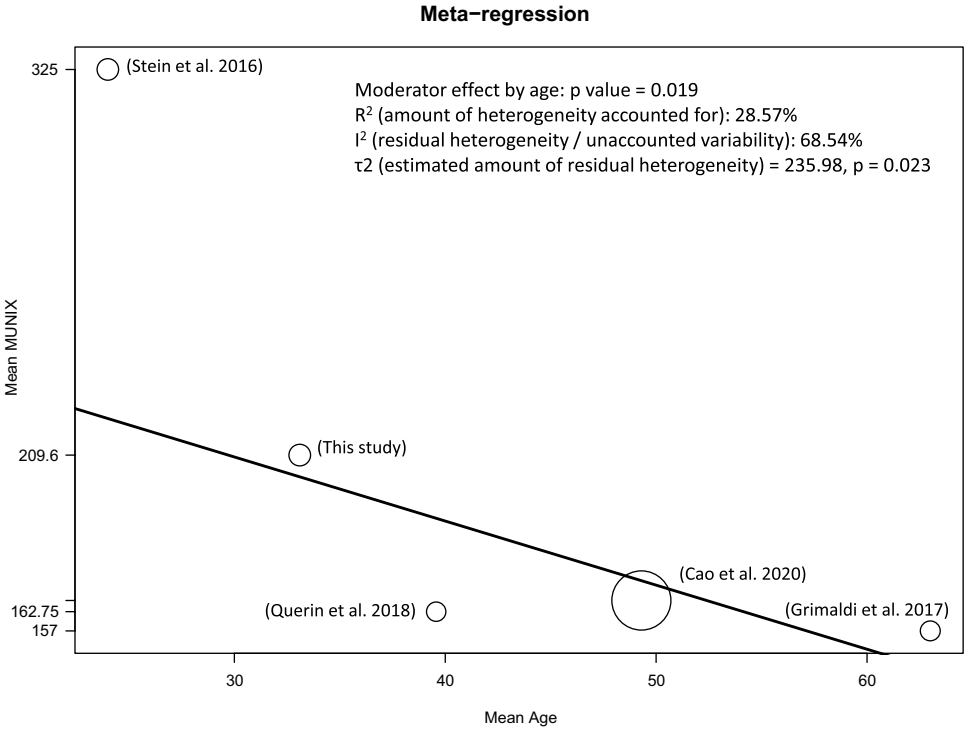

Figure 2: Mean MUNIX of the upper trapezius was significantly moderated by mean age across four published studies, in addition to data from this study. Mixed effect meta-regression model was fitted with DerSimonian-Laird estimator for τ^2.

the heterogeneity across studies and outlier mean and SD values reported by Stein et al.[7] These authors enrolled a younger sample and employed a continuous SIP sampling method at gradually increasing voluntary muscle contraction with post hoc extraction of shorter-length epochs, contrary to the recommended stepwise SIP recording protocol. Also, mean age variance modulated MUNIX-Trapezius and contributed to in-between study heterogeneity. At an individual level, Cao et al.[8] reported variability in MUNIX-Trapezius, as well as MUNIX biceps brachii, within age groups below 60 years, while MUNIX tibialis anterior and abductor pollicis brevis were stable up to the 60-year group. Future studies should further explore motor unit changes in proximal muscles in younger adults.

Following the guidelines for MUNIX acquisition,[4] MUNIX recorded at the UTrap in our sample of control participants had reliable test–retest performance between a novice and senior

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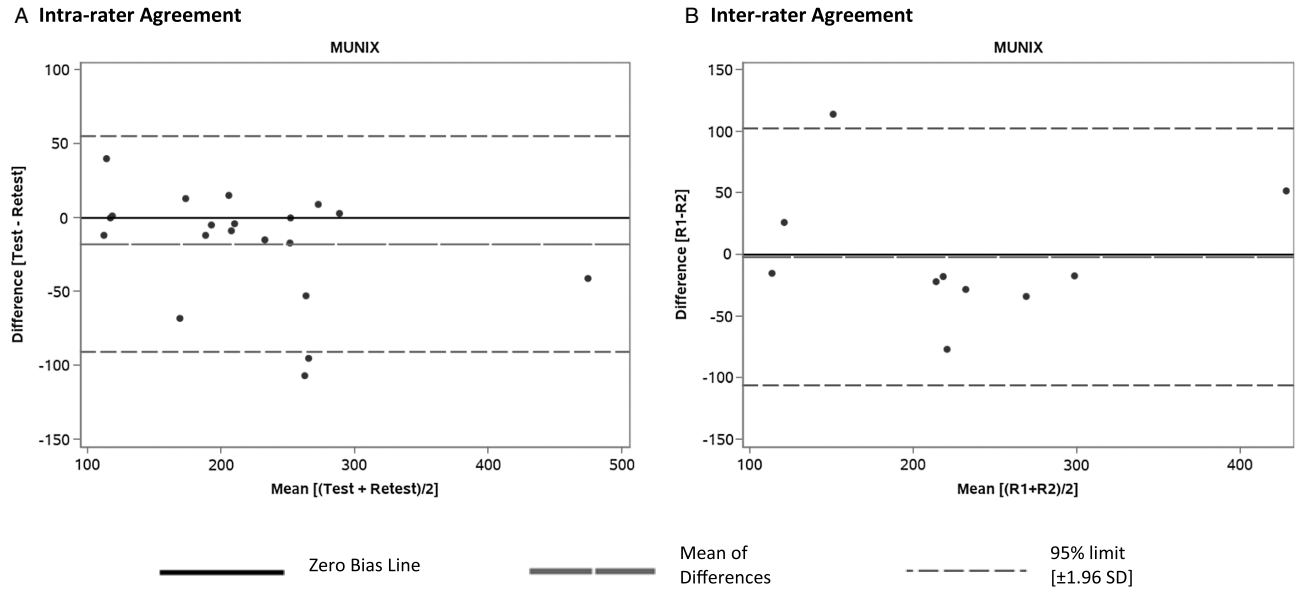

Figure 3: Bland Altman plots of intra- and inter-rater agreement. (A) Intra-rater agreement of MUNIX scores from Rater 1 test and re-test sessions. (B) Inter-rater agreement of MUNIX scores from Rater 1 test and Rater 2 test sessions. This plot would suggest that test-retest differences exceeding 50% CoV are likely more than that expected from test variability alone.

rater. This indicates the robustness of the measure and supports its use in multicentre studies where varying degrees of MUNIX expertise is expected.[3] Test–retest reproducibility was excellent when performed by a novice rater in our enrolled sample, further supporting studies with longitudinal measures as previously reported by Cao et al.[8] While the inter- and intra-rater ICCs from healthy controls represent intrinsic technical variability, future studies should reassess MUNIX-Trapezius reproducibility in disease populations to account for potential patient-specific factors.

MUNIX of the trapezius as a bulbar LMN measure in ALS is a promising alternative to facial nerve-innervated muscles. The trapezius is less susceptible to a floor effect since its supramaximal CMAP – a key component for MUNIX calculation – is larger compared to CMAP from facial muscles. Moreover, in ALS, trapezius activation is relatively preserved until advanced stages, allowing for feasible SIP recording as the disease progresses. It can also be performed with patients seated upright and wearing non-invasive ventilation masks, avoiding the need for wheelchair transfers or interruption of non-invasive ventilation. While cross-sectional MUNIX comparisons could discriminate patients with ALS from controls,[5,7] longitudinal construct validity studies correlating MUNIX to trapezius and clinical measures of speech and swallowing in patients with and without bulbar symptoms are required. Advanced speech assessment tools, such as speech-and-pause analysis of spoken passage recordings,[10] can anchor bulbar function to correlate with MUNIX to trapezius measures over time.

Limitations of this study include the small sample size which reduces the precision of the pooled estimates and meta-regression inferences. The generalizability of our data is limited given the small and younger sample of controls from a single site, despite our intra-rater ICC yielding similar findings to previous studies. Given its motor innervation, determining whether MUNIX-Trapezius reflects an adequate proxy for bulbar function is also limited without further investigation.

In conclusion, MUNIX to upper trapezius in healthy volunteers is a reliable measure with excellent inter- and intra-rater reproducibility. With further longitudinal construct and pharmacological surrogacy validation studies, this measure can serve as a reliable biomarker of bulbar region LMN function in patients with ALS.

Supplementary Material. To view supplementary material for this article, please visit http://dx.doi.org/10.1017/cjn.2023.20.

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Conflict of Interest. The authors have no conflicts of interest to declare.

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