Detection of early motor involvement in diabetic polyneuropathy using a novel MUNE method – MScanFit MUNE

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ARTICLE INFO

HIGHLIGHTS

- MScanFit MUNE yields detailed information on motor unit loss.
- Motor involvement in diabetic neuropathy may be present as early as sensory involvement.
- MScanFit MUNE provides sensitive detection of motor involvement in diabetic polyneuropathy.

ABSTRACT

Objective: Detection of motor involvement in diabetic polyneuropathy (DPN) by nerve conduction studies (NCS) does not occur until there is substantial loss of motor units, because collateral reinnervation maintains compound muscle action potential (CMAP) amplitude. Motor unit number estimation (MUNE) methods may therefore be more sensitive. This study was undertaken to test whether the novel method, MScanFit MUNE (MScan) can detect motor involvement in DPN despite normal NCS.
Methods: Fifty-two type-2 diabetic patients and 38 healthy controls were included. The median nerve was examined in all participants using standard NCS and a detailed CMAP scan, used for MScan. Additional lower extremity NCS in patients were used for DPN diagnosis.
Results: Of 52 diabetic patients, 21 had NCS-defined DPN while lower extremity NCS were normal in 31 patients. MScan motor unit number and size showed higher sensitivity and incidence of abnormality than motor NCS parameters, and a similar sensitivity to sensory NCS.
Conclusions: MScan is able to detect motor axonal damage at times when collateral reinnervation limits NCS changes.
Significance: MScan is a sensitive method to detect motor involvement in DPN, which our data suggests is present as early as sensory.

1. Introduction

The global number of diabetic patients is estimated to increase from 382 million in 2013 to 592 million by 2035 (Guariguata et al., 2014). Over half of all diabetic patients will develop neuropathy in their lifetime. The most common type of diabetic neuropathy is the length-dependent symmetrical neuropathy. This type is dominated by sensory symptoms such as loss of sensation, tingling or pain, where symptoms usually progress from the extremities, proximally (Feldman et al., 2017). In the later stages, motor nerve fibers are affected in the same areas as the sensory neurons (Dyck et al., 2011). This displacement in time could be due to collateral reinnervation, where unaffected motor axons take over innervation of muscle fibers from affected axons. This would give a buffer period, where motor neuron damage would not be detectable as a decrease in force in clinical examination or as a decrease in CMAP amplitude in nerve conduction studies (NCS). It has been shown that these changes are not detectable until 50% of motor axons are lost, but the current diagnostic tools for diabetic neuropathy rely on these measures (Hansen and Ballantyne, 1978; Daube, 2006).

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There are no available methods that allow for direct measurement of the exact motor unit number. Instead, motor unit number estimation (MUNE) methods have been developed (McComas et al., 1971; Mekras et al., 1992; Doherty et al., 1993; de Carvalho et al., 2018). MUNE methods have been shown to be better suited than any other electrophysiological test for motor unit loss, but none of the methods have found regular use in clinics. Current methods are prone to bias by the examiner, based on a small sample to represent all motor units and time consuming in examination and analysis.

MScanFit MUNE (MScan) is a new MUNE method, developed to avoid some of the limitations of previous MUNE methods. MScan estimates the number of motor units by fitting a statistical model to a detailed stimulus-response curve, or 'CMAP scan' (Bostock, 2016). In recent studies, MScan has been shown to be a fast, sensitive and reproducible method, which may be helpful in diagnoses and monitoring disease progression in neuromuscular disorders, particularly amyotrophic lateral sclerosis (ALS) (Jacobsen et al., 2017). So far the only published study of MScan in neuropathy has been one on multifocal motor neuropathy, which showed decreased MUNE values and increased motor unit sizes, whereas CMAP amplitudes were well-preserved (Garg et al., 2017). MScan has not previously been tested in diabetic neuropathy.

Our aim with this study was to examine the utility of MScan in detecting motor unit loss in DPN and compare MScan with conventional NCS in this regard.

2. Methods

2.1. Participants

Fifty-two patients were included (12 female 40 male, age 34–84, mean 62.9). These were compared to 38 healthy control subjects (18 female, 20 male, age 33–76, mean 60.0). Initial recruitment followed that of a larger study that will be published later. These patients were recruited from the DD2 cohort, a database of Danish type 2 diabetic patients diagnosed after 1st of January 2009. We recruited from the 5755 patients who responded to a questionnaire sent to 6726 of the DD2 cohort (more details at https://dd2.nu). Initial recruitment was solely based on postal code, but due to majority of patients without diabetic polyneuropathy, we recruited additional patients based on a Michigan neuropathy screening instrument (MNSI) score (questionnaire part) ≥ 4 (Feldman et al., 1994). We enrolled 55 patients consecutively from the DD2 cohort from January 2017 to July 2017. Of these, 13 patients were excluded due to self-reported history, symptoms or electrophysiological signs of carpal tunnel syndrome. Preliminary results of the remaining 42 patients revealed too few patients with NCS confirmed neuropathy (12 of 43), and therefore we later supplemented with 9 more patients with DPN and without signs of CTS recruited as part of another large study, also soon-to-be published. These participants were diabetic patients recruited from the clinic – already diagnosed with neuropathy.

The patients all received a neurological examination and were each given a MNSI score and a neurological impairment score of the lower limbs (NIS-LL).

All participants signed a consent form after written and oral information about each procedure. The study protocol was approved by the Regional Committee on Health Research Ethics and the Danish Data Protection Agency.

2.2. Nerve conduction studies (NCS)

All patients were examined with a Keypoint.net EMG machine. NCS on the right peroneal, tibial, bilateral sural and the right median nerve were performed on all patients using surface electrodes in accordance with department's protocols. In the event of abnormal median nerve, the right ulnar nerve was also examined. In healthy subjects, only median and ulnar NCS were performed.

Prior to application of the surface electrodes, the participant's skin was prepared with an abrasive gel and cleaned with alcohol swabs. Throughout the examination, skin temperature was maintained between 32 and 36 °C.

The evaluated motor NCS parameters were distal motor latency (DML), motor conduction velocity (CV), CMAP amplitude and minimum F-wave latency; sensory NCS parameters were sensory CV and sensory nerve action potential (SNAP) amplitude.

2.2.1. Peroneal NCS

The recording electrode was placed over the bulk of m. extensor digitorum brevis. Distal stimulation was done at the ankle 90 mm proximal from the recording electrode. Proximal stimulation was done 2 cm distal to capitulum fibulae.

2.2.2. Tibial NCS

Recording electrode placement was over the bulk of the m. abductor hallucis muscle. The distal stimulation site was 90 mm proximal from the recording electrode, below the medial malleolus and the proximal stimulation site was in the popliteal fossa.

2.2.3. Sural NCS

Placement of the recording electrode was between the lateral malleolus and the Achilles tendon. The stimulation site was 130 mm from the recording electrode, proximally at sura.

2.2.4. Median NCS

For motor NCS, the recording electrode was placed over the abductor pollicis brevis (APB) muscle and the reference over the distal part of the first metacarpal bone. The distal stimulation site was 67 mm from the recording electrode, between the flexor carpi radialis and palmaris longus tendons. The proximal stimulation site was at the elbow, medial to the m. biceps brachial tendon.

For sensory NCS, the nerve was stimulated at the wrist and SNAP was recorded antidromically from the second digit using ring electrodes.

2.2.5. Ulnar NCS

For motor NCS, placement of the recording electrode was over the abductor digiti minimi muscle and the reference over the distal part of the fifth metacarpal. The distal stimulation site was 65 mm proximally from the recording electrode, radially to the m. flexor carpi ulnaris tendon. The proximal recording site was 3–5 cm distal to the olecranon and epicondylus lateralis.

For sensory NCS, the nerve was stimulated at the wrist and SNAP was recorded antidromically from the fifth digit using ring electrodes.

2.3. MScanFit MUNE (MScan)

MScan examinations consist of two parts. The recording and the analysis. The recording is a detailed CMAP scan of a motor nerve. The examiner starts the program at supramaximal stimulation, and the program is set to decrease the stimulation gradually by 0.2% of the previous stimulation every 0.6 s. This part takes between 5 and 10 min depending on the muscle examined.

The CMAP scan is performed using standard surface recording electrodes and adhesive stimulating electrodes. These are connected to a Digitimer Ltd D440 preamplifier and DS5 stimulator respectively. The amplified signal is filtered through a HumBug 50 Hz noise eliminator. The filtered signal is sent to a computer running the QTracS Software (written by H. Bostock, copyright

Institute of Neurology, University College London, UK). We used the MScan part of the TRONDNF recording protocol.

The CMAP scan was conducted on the APB muscle, stimulating the median nerve 65–70 mm from the recording site. Prior to the examination, we ensured that the electrode was placed over the APB where the amplitude was the highest.

To analyze the CMAP scan, we used MScanFit, featured in the QTracP software. This is an automated process, apart from choosing the start- and endpoints of the CMAP scan, possible on a standard PC. The analysis will provide results on motor unit number and motor unit size. The evaluated MScan parameters were: (1) the MScan MUNE value, which is the estimated number of functional motor units in the muscle, (2) N50, which is the estimated number of larger units making up 50% of the CMAP amplitude; (3) the largest unit (%), which is the size of the largest unit expressed as a percentage of the maximum CMAP amplitude. (4) A50 (%), the smallest amplitude of the units making up the N50 larger units, expressed as a percentage of the maximum CMAP amplitude, and (5) A50 (μV) the absolute amplitude of the N50th largest unit. N50 behaves like MUNE, but is immune to the problem of distinguishing very small units from noise. A50 (μV) provides a measure sensitive to collateral reinnervation, while A50 (%) and Largest unit (%) are increased by reduction in CMAP amplitude as well as by collateral reinnervation.

2.4. Statistical analysis

Statistical calculations were performed in the QtracP software. Comparison of means was performed with unpaired t-test. To test for normality we used Lilliefors test. Sensitivity, specificity and the best cut-off value to maximize the accuracy (mean of sensitivity and specificity) for discriminating patients from healthy controls were calculated. Results with $P < 0.05$ were considered significant. The ability of a method to discriminate DPN patients from controls was evaluated with receiver operating characteristic (ROC) analyses, by determining the area under the curve (ROC-AUC).

3. Results

3.1. Polyneuropathy diagnosis

The neuropathy diagnosis was based on lower extremity NCS using Dyck's criteria, which requires at least one abnormal parameter across two nerves, one of which should be the sural nerve – when compared to laboratory controls (Dyck et al., 2011). We divided the patients into two groups according to NCS of the lower extremities. One group of type 2 diabetic patients without neuropathy (DPN−) and a group of type 2 diabetic patients with distal symmetrical polyneuropathy (DPN+). The DPN+ group included 21 patients (19 male, 2 female, age 48–84, mean 65.5), the DPN− group included 31 patients (21 male, 10 female age 34–76, mean 61.2). The mean NIS-LL (0–88) for the DPN− group was 3.645, and for the DPN+ group 12.06. Mean MNSI score (0–10) was 2.067 for the DPN− and 5.281 for the DPN+ group.

3.2. MScan and NCS results between groups

Comparing the DPN+ group to the DPN− and healthy control groups, there was a significant difference in the mean of all MScan and NCS parameters between DPN+ patients and healthy controls and between DPN+ and DPN− patient groups (Table 1, Figs. 1 and 2). There was no significant difference between healthy controls and DPN− patients (Table 1).

3.3. Sensitivity and specificity of MScan and NCS parameters in the median nerve

The ability of MScan and NCS parameters to discriminate DPN+ group from healthy controls using ROC analysis are shown in Table 2 and Fig. 3A, while discrimination between the DPN− group and healthy controls is shown in Table 3 and Fig. 3B. When using the cut-off value that produces the highest accuracy, the accuracy of MScan unit number and size parameters were comparable with NCS parameters. The area under the ROC curve, or AUC, provides a convenient overall measure of discrimination, and SNAP amplitude provided the highest AUC as well as the highest accuracy of the NCS parameters. It is notable that all four of the MScan parameters in Table 2 provided AUC values comparable to SNAP amplitude, and all four provided higher AUC values than all of the motor NCS parameters. When looking at DPN− patients, the area under the ROC curve and accuracy were low for both MScan and NCS parameters (Table 3 and Fig. 3b).

Between 14.3 and 52.4% of DPN+ patients had abnormal scans (i.e. with measurements outside the 95% confidence limits for healthy controls) according to MScan analysis, whereas the highest abnormality for NCS was achieved for motor CV (33.3%). In contrast, and in spite of the difference in mean values, the sensory NCS parameters were only abnormal by this criterion in 9.5% of DPN+ patients.

3.4. Correlation with clinical and biochemical measures

We examined the relation of the estimated number of motor units with NIS-LL, MNSI and HbA1c to compare our findings with other measures of neuropathy severity, but none of the correlations were statistically significant: for MScan MUNE v HbA1c, $R = 0.021$, $P = 0.86$; MScan MUNE v .NIS-LL, $R = -0.21$, $P = 0.15$; MScan MUNE v MNSI, $R = -0.25$, $P = 0.085$.

4. Discussion

The main finding of this study is that MScan is more often abnormal than all sensory and motor NCS parameters including CMAP amplitude. We have shown that MScan provides sensitive detection of diabetic motor neuropathy.

4.1. Is motor involvement a late stage phenomenon in diabetic neuropathy?

Diabetic neuropathy has been suggested to be primarily a sensory neuropathy and that motor involvement develops in the later stages in the same areas as the sensory (Dyck et al., 2011). In this study, we hypothesized that this apparent delay might be due to collateral reinnervation, since initial motor neuron damage would not be detectable, either as a decrease in strength in clinical examination or as a decrease in CMAP amplitude in NCS, until about 50% of motor units are lost (Daube, 2006). For this reason, we used a novel MUNE method, which can detect motor unit loss in the presence of collateral reinnervation.

Our results support this hypothesis; at least as far as upper limb nerves are concerned. In ROC analyses, for discriminating DPN+ patients from healthy controls, we found that the AUCs for MScan, motor unit number and size parameters were higher than those for motor NCS and similar to that for SNAP amplitude. MScan parameters also showed a higher incidence of abnormality (up to 52.4%) than both sensory and motor NCS. These results indicate that there is a loss of motor axons at times when NCS are unable to detect motor neuron involvement. The significant changes in motor unit size suggest that collateral reinnervation has taken place, which could mask the motor axon changes in earlier stages of DPN. Of

Table 1
MScan and Nerve Conduction Studies (NCS): differences between groups.

	Healthy controls	DPN−	DPN+	Controls v DPN−	Controls v DPN+	DPN− v DPN+
	Mean (±SE)			P-Value		
MScan motor unit number and size parameters						
MUNE	117.8 (5.1)	113.3 (6.8)	75.7 (5.7)	0.59	**6.0×10^{-6}**	**0.00030**
N50	33.6 (1.9)	30.8 (2.1)	19.1 (1.8)	0.32	**1.2×10^{-5}**	**0.00026**
Largest unit (%)	3.76 (0.21)	4.34 (0.38)	6.99 (0.91)	0.157	**6.5×10^{-5}**	**0.0040**
A50 (%)	1.08 (0.05)	1.23 (0.10)	1.94 (0.17)	0.17	**4.9×10^{-7}**	**0.00043**
A50 (μV)	110.9 (6.3)	123.2 (10.2)	136.1 (7.5)	0.29	**0.015**	0.356
NCS parameters of the median nerve						
CMAP peak (mV)	10.47 (0.40)	10.33 (0.47)	7.81 (0.63)	0.80	**0.00054**	**0.0021**
DML (ms)	3.47 (0.06)	3.43 (0.06)	3.90 (0.11)	0.58	**0.00055**	**0.00021**
Motor CV (ms^{-1})	53.6 (0.5)	54.1 (0.7)	49.5 (1.0)	0.57	**0.00013**	**0.00019**
F-wave latency (ms)	29.2 (0.4)	28.9 (0.4)	32.3 (0.6)	0.67	**0.00011**	**1.6×10^{-5}**
Sensory CV (ms^{-1})	56.5 (1.0)	58.0 (0.9)	51.8 (1.5)	0.27	**0.0098**	**0.00068**
SNAP amplitude (μV)	18.8 (1.4)	17.7 (1.7)	8.6 (1.5)	0.640	**5.8×10^{-5}**	**0.00057**

Differences between healthy controls and two patient groups by MScan and NCS. CV = Conduction velocity, CMAP = Compound muscle action potential, DML = Distal motor latency, SNAP = Sensory nerve action potential.
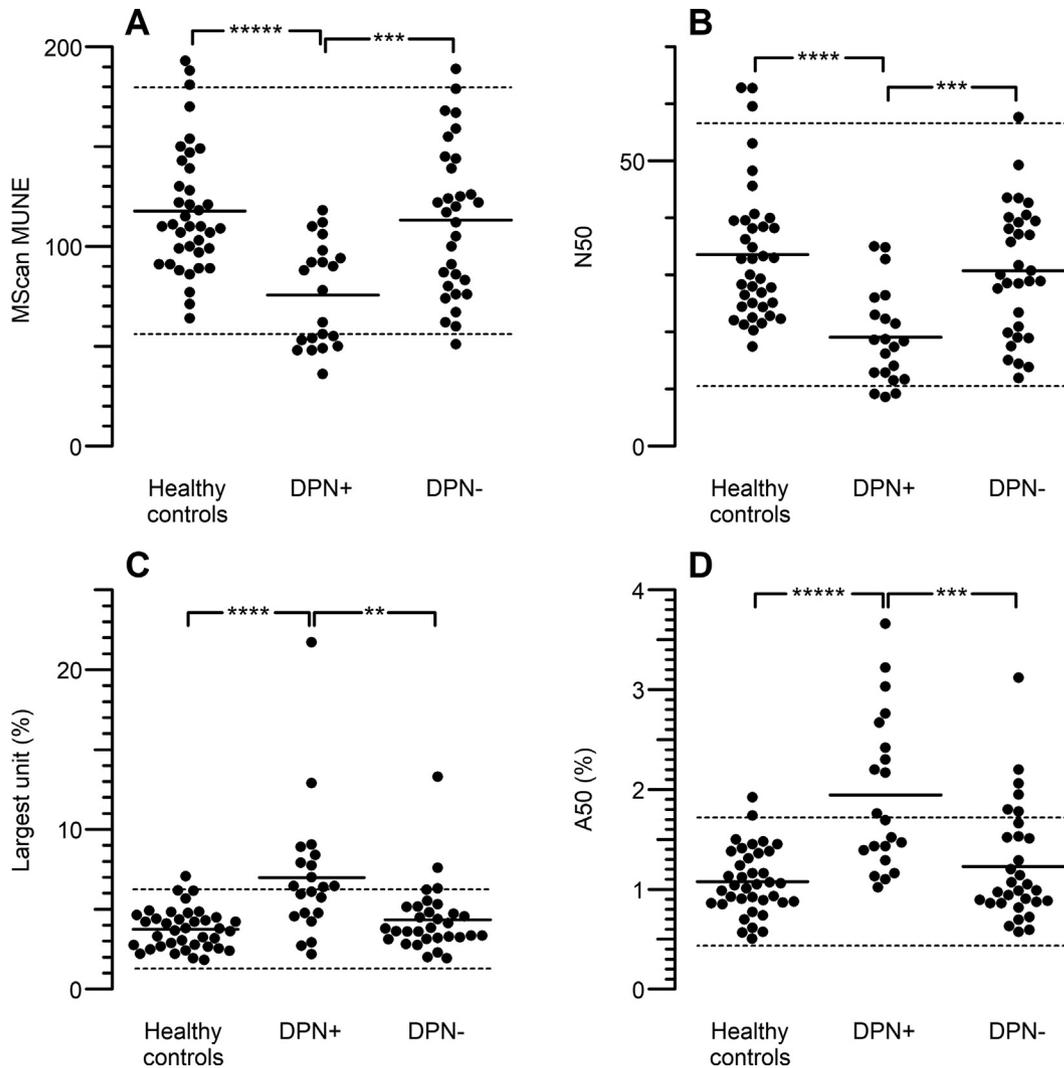

Fig. 1. Distributions of MScan parameters between the 38 healthy controls, 21 patients with diabetic polyneuropathy (DPN+) and 31 patients without neuropathy (DPN−). The asterisks indicate the P values for comparison by the *t*-test, as listed in Table 1 (** = P < 0.01, *** = P < 0.001,**** = P < 0.0001, ***** = P < 0.00001). Horizontal solid lines indicate means, and dashed lines indicate 95% confidence limits for the healthy subjects. The ability of these 4 measurements to discriminate between healthy controls and DPN+ patients are provided by ROC analysis in Table 2.

the two measures of motor unit size produced by the MScanFit program, only A50 (μV) provides evidence of an absolute increase in motor unit size in DPN+ patients. This increase was small (23%),

but significant (Table 1), and most likely underestimates the degree of collateral reinnervation, since unit expansion was being counteracted by denervation.
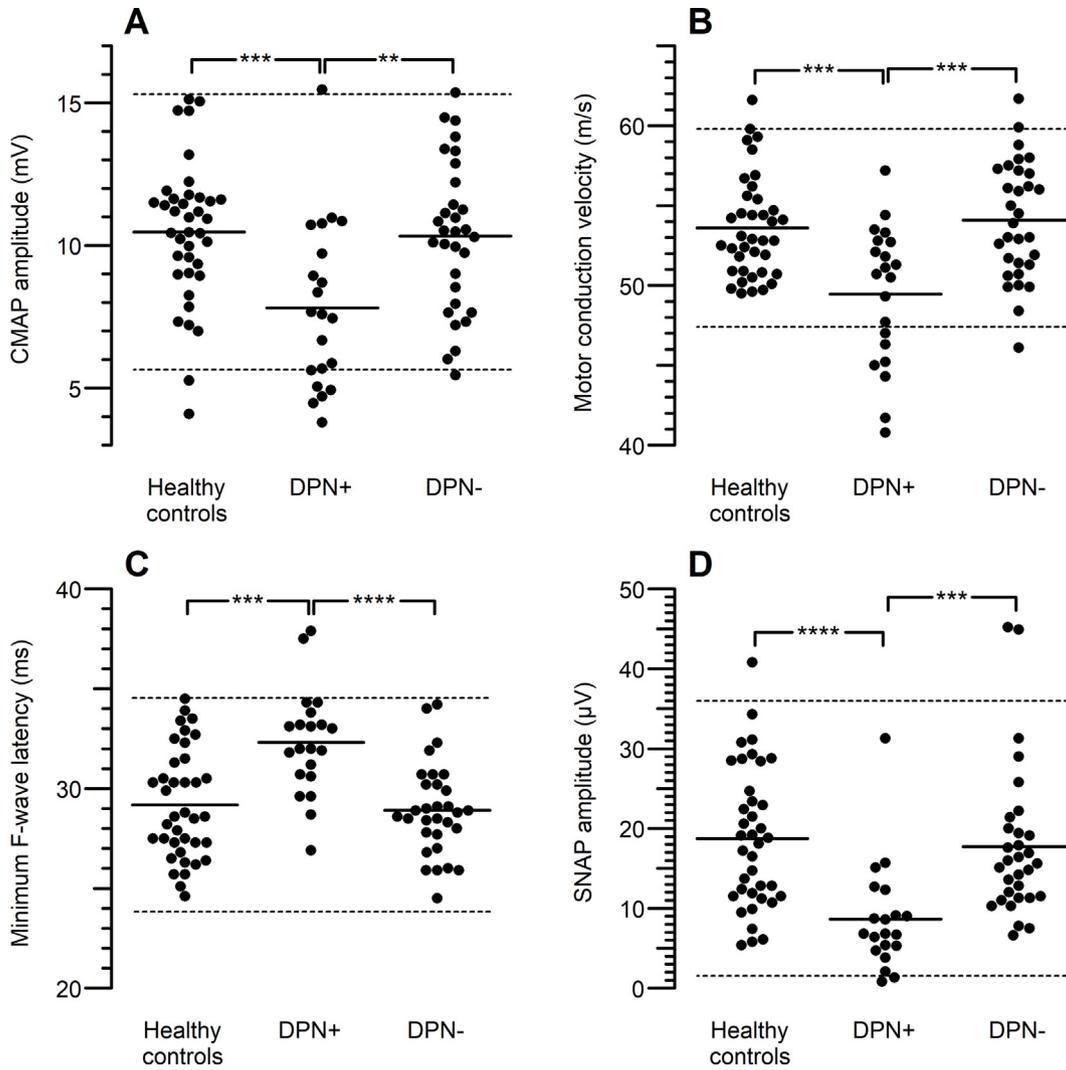
Fig. 2. Distributions of nerve conduction study parameters between the 38 healthy controls, 21 patients with diabetic polyneuropathy (DPN+) and 31 patients without neuropathy (DPN−). CMAP = Compound muscle action potential, SNAP = Sensory nerve action potential. The asterisks indicate the P values for comparison by the t-test, as listed in Table 1 (** = P < 0.01, *** = P < 0.001, **** = P < 0.0001). Horizontal solid lines indicate means, and dashed lines indicate 95% confidence limits for the healthy subjects. The ability of these four measurements to discriminate between healthy controls and DPN+ patients are provided by ROC analysis in Table 2.

Table 2
Discrimination by ROC analysis between healthy controls and diabetic patients with neuropathy.

	Cut-off for max. accuracy	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	% Abnormal
MScan						
MUNE	98.5	81.0	73.7	76.3	0.840	42.9
N50	19.49	61.9	97.4	84.7	0.862	14.3
Largest Unit (%)	5.7	66.7	92.1	83.1	0.825	52.4
A50 (%)	1.385	76.2	81.6	79.7	0.872	47.6
Nerve conduction studies						
CMAP peak (mV)	8.935	71.4	81.6	78.0	0.779	28.6
DML (ms)	3.735	71.4	68.4	69.5	0.764	14.3
Motor CV (ms^{-1})	49.4	42.9	100	79.7	0.754	33.3
F-wave latency (ms)	30.55	81.0	73.7	76.3	0.791	9.5
Sensory CV (ms^{-1})	52.05	60.0	73.7	69.0	0.695	9.5
SNAP amplitude (μV)	9.3	75.0	89.5	84.5	0.869	9.5

Cut-offs, sensitivity and specificity for optimal accuracy and area under ROC curve for discriminating DPN+ patients from healthy controls by MScan and NCS measurements. CV = Conduction velocity, CMAP = Compound muscle action potential, DML = Distal motor latency, SNAP = Sensory nerve action potential.

Correlation with clinical findings did not reveal any significant relation to the estimated number of motor units. This could have provided further evidence that the changes we find in MUNE value were indeed connected to the severity of neuropathy. The absence of any correlation with HbA1c could be explained by glucose lowering treatment intensifying with severity of neuropathy.

Further studies, examining MScan in a foot muscle compared to sensory and motor NCS, are necessary to test the well-accepted
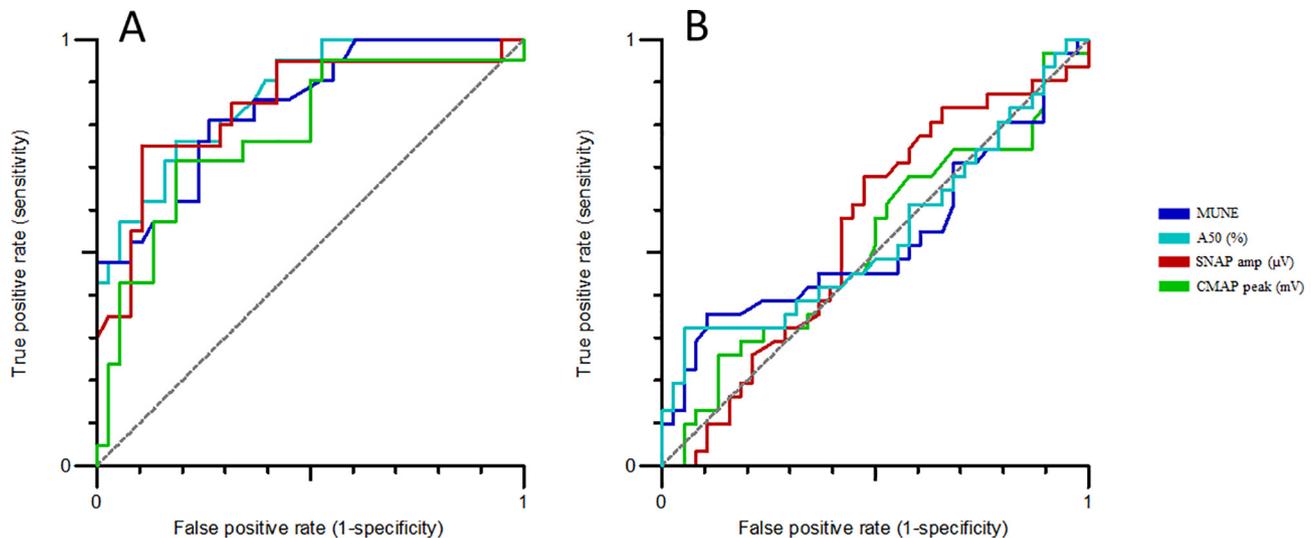
Fig. 3. ROC curves of MScan and NCS parameters' ability to discriminate between (A) healthy controls and DPN+ patients, (B) healthy controls and DPN− patients.

Table 3
Discrimination by ROC analysis between healthy controls and diabetic patients without neuropathy.

	Cut-off for max. accuracy	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	% Abnormal
MScan						
MUNE	87.5	35.5	89.5	65.2	0.563	3.2
N50	21.1	29.0	94.7	65.2	0.547	0
Largest Unit (%)	3.0	83.9	36.8	58.0	0.580	6.5
A50 (%)	1.5	32.3	94.7	66.7	0.543	19.4
Nerve conduction studies						
CMAP peak (mV)	7.95	25.8	86.8	59.4	0.524	3.2
DML (ms)	3.78	87.1	31.6	56.5	0.549	0
Motor CV (ms^{-1})	55.75	41.9	78.9	62.3	0.553	3.2
F-wave latency (ms)	30.25	77.4	42.1	58.0	0.510	0
Sensory CV (ms^{-1})	56.15	64.5	57.9	60.9	0.588	0
SNAP amplitude (µV)	18.0	67.7	52.6	59.4	0.551	0

Cut-offs, sensitivity and specificity for optimal accuracy and area under ROC curve for discriminating DPN− patients from healthy controls by MScan and NCS measurements.
CV = Conduction velocity, CMA*P* = Compound muscle action potential, DML = Distal motor latency, SNA*P* = Sensory nerve action potential.

hypothesis that diabetic neuropathy starts in sensory nerves and that motor nerves are only involved in later stages. Our results suggest otherwise, although we only examined a distal upper extremity nerve. We propose that the motor involvement in diabetic neuropathy, both clinically and electrophysiologically, is often overseen due to collateral sprouting.

4.2. MScan MUNE can sensitively detect motor involvement in diabetic neuropathy

We found a lower number of motor units for the DPN+ group than the DPN− and control groups. To date, MUNE has been examined in diabetic patients in only a few studies. When 6 diabetic patients were compared to 6 healthy subjects, lower motor unit numbers were estimated by decomposition-enhanced spike-triggered averaging MUNE in anterior tibial muscle in diabetic patients (Allen et al., 2013). Later, the same authors found, in 12 diabetic patients compared to 12 healthy subjects, reduced muscle strength and decreased cross-sectional area of anterior tibial muscle by magnetic resonance imaging, in addition to decreased MUNE values in diabetic patients (Allen et al., 2014). In another study, multipoint stimulation MUNE was applied to extensor digitorum muscle in 51 asymptomatic type 1 diabetic children. Sensory and motor NCS did not differ between patients and 21 healthy children

whereas MUNE values were lower in diabetic patients. However, the increase in unit sizes was not significant in that study (Toth et al., 2014). In contrast to these studies, we examined an upper extremity nerve. Although median nerve is expected to be affected in rather late stages of DPN, we found pronounced decrease in motor unit estimates using MScan MUNE together with increased unit sizes. We compared MScan results to motor and sensory NCS, all examined in the median nerve, and found more pronounced changes in MScan than motor NCS in patients with DPN. As expected, neither MScan nor NCS parameters could discriminate healthy controls and diabetic patients without neuropathy.

In our examination of MUNE results as classifiers, estimated number of motor units as well as unit sizes could have a place in detecting motor nerve damage in diabetic patients – but is not a replacement for NCS.

4.3. Limitations

This study has a number of limitations. Firstly, the muscle that we examined is not expected to be involved until late stages of diabetic neuropathy, due to the length-dependent nature of the disease. If we examined a distal muscle in lower extremities, we would probably find more pronounced changes. Muscles such as

the extensor digitorum brevis can be very unpleasant to examine with CMAP scan due to the high stimulation intensity required. Secondly, the number of patients with DPN was less than we had expected, and we needed to supplement participants from different cohorts to balance the group sizes. The small sample size also limited our ability to divide patients further into groups based on certainty of diagnosis, which would result in groups too small for analysis. Moreover, we did not have NCS results from lower extremity nerves for our healthy controls and the present study is based only on patients with large fiber neuropathy. We excluded patients with carpal tunnel syndrome using clinical and electrophysiological examinations, but did not perform ultrasound recordings to this end, which may have biased our results.

4.4. Conclusions and future research

In the present study, we have found early changes in the motor axons of the median nerve, commonly thought to be affected in the late stages of DPN only. Additionally, we have found signs that suggest collateral reinnervation could be the cause of delayed detection of the motor axon changes. We have shown that MScanFit MUNE provides more information about motor axon degeneration than conventional NCS. Extension of these observations to lower limb nerves would further support the hypothesis that the apparently lower susceptibility of motor axons to DPN is attributable to collateral reinnervation.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgments

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