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## REPEATABILITY OF NERVE CONDUCTION MEASUREMENTS USING AUTOMATION

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**ABSTRACT. Objective.** To quantify nerve conduction study (NCS) reproducibility utilizing an automated NCS system (NC-stat<sup>®</sup>, NeuroMetrix, Inc.). **Method.** Healthy volunteers without neuropathic symptoms participated in the study. Their median, ulnar, peroneal, and tibial nerves were tested twice (7 days apart) by the same technician with an NC-stat<sup>®</sup> instrument. Pre-fabricated electrode arrays specific to each nerve were used. Both motor responses (compound motor action potential [CMAP] and F-waves – all nerves) and sensory responses (sensory nerve action potentials [SNAP] – median and ulnar nerves only) were recorded following supramaximal stimuli. Automated algorithms determined all NCS parameters: distal motor latency (DML), mean F-wave latency (FWL), distal sensory latency (DSL), CMAP amplitude, and SNAP amplitude. Latency was adjusted for skin temperature deviation from reference. Pearson correlation coefficient (CC), intraclass correlation coefficient (ICC), coefficient of variance (CoV), and relative intertrial variation (RIV) were calculated. **Results.** Fifteen subjects participated in either upper or lower extremity studies with nine participating in both. With the exception of CMAP amplitude, all parameters had CoV less than 0.06. Upper extremity amplitude parameters had CCs greater than 0.85. CCs for latencies were greater than 0.80 except for the median nerve FWL (CC = 0.69). For lower extremity nerves, ICCs were highest for mean FWL (>0.90), followed by DML (>0.82) and then CMAP (peroneal 0.33, tibial 0.73). The 10th to 90th RIV percentiles were bounded by  $\pm 7\%$  for F-wave latencies;  $\pm 9\%$  for all DSLs; and  $\pm 11\%$  for DML (except peroneal at 15%). **Conclusions.** The reproducibility of NCS parameters obtained with an automated NCS instrument compared favorably with traditional electromyography laboratories. F-wave latencies had the highest repeatability, followed by DML, DSL, SNAP and CMAP amplitude. Given their high reproducibility, automated NCS instrument may encourage wider utilization of NCS in clinical and research applications.

**KEY WORDS.** nerve conduction study, repeatability, automation, CMAP, F-wave, SNAP

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## INTRODUCTION

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Nerve conduction studies (NCS) are an objective, quantitative, and reproducible measure of peripheral nerve function and are widely used in the diagnosis of neuropathies [1, 2]. They can be used to monitor neuropathic disease progression [3] and the efficacy of interventions in clinical trials [4]. However, non-uniform electrophysiologic test procedures degrade reproducibility. Potential sources of variation include the use of different EMG

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instruments at different test sessions or sites [5], inconsistent placement of recording and stimulating electrodes [6], use of non-standardized distance measurements, use of sub-maximal electrical stimuli, poor skin preparation resulting in high skin impedance, and failure to maintain limb temperature within an acceptable range or to compensate for temperature. All these factors may compromise the repeatability of NCS measurement and lead to erroneous diagnostic conclusions.

Aside from true physiological changes, factors that influence repeatability of NCS measurements are broadly grouped into two categories: inter-tester variability and intra-tester variability. Inter-tester variability refers to variability of a test parameter measured on a single individual when repeat test measurements are made by two or more examiners. Intra-tester variability refers to variability of a test parameter when repeat test measurements are made by a single examiner. In the absence of physiological changes, both inter-tester and intra-tester variability are influenced by electrodiagnostic examination technique. Automated NCS instruments may improve NCS repeatability by utilizing prefabricated electrode arrays and automating evoked waveform analysis [7]. The objective of this study is to quantify NCS repeatability utilizing the NC-stat<sup>®</sup> (NeuroMetrix, Inc., Waltham, Massachusetts), an automated NCS system [8–10]. We hypothesized that use of the NC-stat system would yield highly reproducible NCS results.

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## METHODS AND MATERIALS

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### *Subjects*

Subjects volunteered for the study and provided written, informed consent. All were healthy office workers who lacked neurological complaints or known causes of peripheral neuropathy. The study was approved and monitored by an independent review board (Copernicus Group, Cary, NC, USA).

### *Nerve conduction studies*

Each upper and lower extremity nerve was tested twice (7 days apart) by the same technician, utilizing the NC-stat<sup>®</sup> (NeuroMetrix, Inc., Waltham, MA, USA), an automated NCS instrument. Shown in Figure 1 is a photograph of the NC-stat system components: pre-fabricated electrode arrays specific to peroneal nerve motor testing; an electronic monitor to be connected to the electrode arrays for nerve stimulation and waveform acquisition and analysis; a communication port to transmit data for report generation. The NC-stat system is FDA

510(k) cleared for the performance of motor studies of the median, ulnar, peroneal and tibial nerves, and sensory studies of the median, ulnar and sural nerves. Tests were performed in a commercial office setting similar to a physician's office where NC-stat systems are typically used. Upper extremity and lower extremity repeatability studies were carried out separately. Each study lasted for about 2 weeks to complete the 7-day interval test-retest protocol for 15 subjects. A technician applied pre-fabricated electrode arrays specific to each nerve based on readily identifiable anatomic landmarks. The electrode arrays incorporated stimulating, recording, and ground electrodes, as well as a temperature sensor. The device automatically checked skin impedance and determined the minimum stimulator current needed to deliver a supramaximal stimulus with amplitude ranging from 10 to 100 mA and duration between 100 and 500  $\mu$ s. The evoked compound muscle (CMAP) or compound sensory nerve (SNAP) action potentials were recorded following a series of supramaximal stimuli. Supramaximal is defined as CMAP amplitudes having less than 10% variation from their mean for three stimuli of increasing intensities (step size varies between 2.5 and 20 mA depending on nerve and stimulus duration). SNAPs are acquired at the motor supramaximal stimulation level since NC-stat recorded both motor and sensory responses simultaneously to minimize overall stimulus count [10]. Time interval between stimuli is about 2–3 s. The technician was trained according to the manufacturer's instructions and was blinded to the prior test results during the retest.

The median stimulator cathode was placed over the midline volar wrist 3 cm proximal to the distal wrist crease. A volume-conducted median motor response generated by abductor pollicis brevis was recorded using paired electrodes placed over the lateral and medial aspects of the distal wrist crease [8]. Concurrently, an antidromic SNAP was recorded from the middle finger using self-adhering ring electrodes placed around the proximal interphalangeal (PIP) joint (active electrode), with the inactive electrode 3 cm distal. The ulnar stimulating cathode was placed over the medial volar wrist 3 cm proximal to the distal wrist crease. The ulnar motor response was recorded using an active electrode placed over abductor digiti minimi and an inactive electrode placed over the lateral volar wrist. The ulnar SNAP was recorded from the small finger with the active electrode over the PIP and inactive electrode 2 cm distal. The stimulator cathode for peroneal testing was placed lateral to the tibia at the intermalleolar line. Responses were recorded using detector pairs placed along a line between the lateral malleolus and the 3rd toe, over the vicinity of the Extensor Digitorum Brevis muscle (see Figure 1). For tibial nerve testing, stimulating cathode was placed over the posterior tibial nerve just posterior to the



Fig. 1. Photograph of the NC-stat instrument. It consists of three components: pre-fabricated electrode arrays (biosensor, left panel) for a peroneal motor nerve conduction study, an electronic monitor (connected to a biosensor during testing), a report generation system (not shown) based on electrophysiological data collected and processed by the monitor and transmitted via “docking station” (a telecommunication port for secure data transfer via telephone line).

medial malleolus. Both the active and inactive electrodes were located just distal to the medial malleolus. The active electrode was anterior and the inactive electrode was

posterior. A ground electrode and temperature sensor were interposed between stimulating and recording electrodes in all cases. At the conclusion of NCS for a given subject, test data were uploaded to a central database.

Sample waveforms are shown in Figure 2. Motor responses (CMAP and F-wave) were recorded with filter settings of 15 Hz high pass and 3 kHz low pass; sensory responses were recorded with 175 Hz high pass and 3 kHz low pass filters. Supramaximal CMAP and SNAP were sampled at 10 kHz and F-waves were acquired at 2.5 kHz. Four CMAP waveforms were acquired for each nerve. For recording SNAPs, 6–15 individual waveforms were averaged depending upon the signal-to-noise ratio. Up to 10 F-wave responses (with 12 traces as a maximum) were recorded for the median and ulnar nerves. Up to 20 peroneal and tibial F-wave responses (with 40 traces as a maximum for peroneal, and 24 traces as a maximum for tibial) were acquired for lower extremity tests.

### NCS Parameters

All NCS parameters were determined by automated computer algorithms [7, 9, 10]. For motor studies, distal motor latency (DML) was the time difference between stimulus onset and initial negative deflection (marked as “+” in the lower left panel of Figure 2). DML values from four CMAP waveforms were averaged and reported

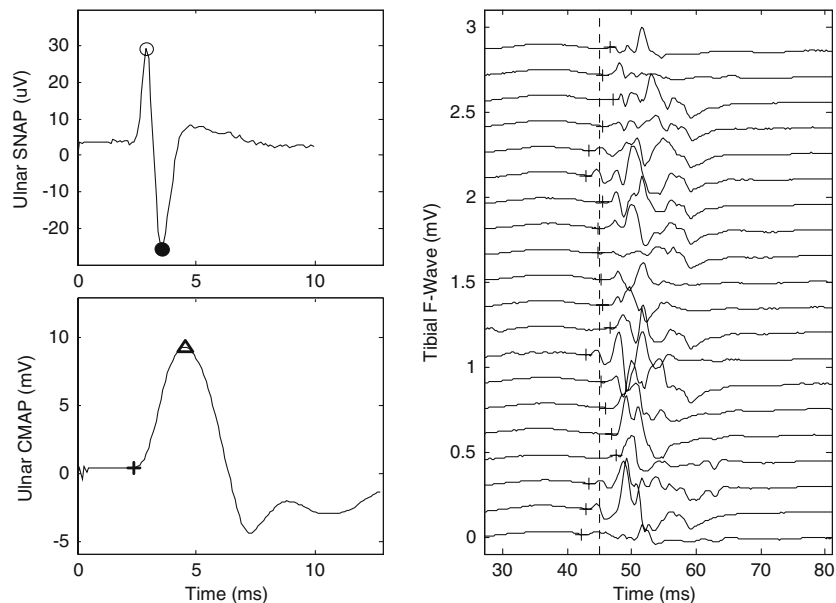


Fig. 2. Sample motor and sensory responses acquired by the NC-stat nerve conduction instrument during the repeatability study for one subject. Top left panel shows the ulnar sensory nerve action potential (SNAP) with distal sensory latency (DSL) marked by an open circle. Bottom left panel shows the ulnar compound muscle action potential (CMAP) with distal motor latency (DML) marked with a plus and negative peak marked with a triangle for peak-to-base amplitude calculation. Right panel shows the tibial F-wave traces. Pluses indicate the NC-stat assigned F-wave latencies for individual traces with F-wave response. Dotted line is the calculated mean F-wave latency for the F-wave set.

(after temperature correction). CMAP amplitude was measured baseline to negative peak (upward deflection, identified by the upper triangle) based on the averaged CMAP. F-wave onset latency was identified for each trace with an identified F-wave response (traces with “+”, right panel of Figure 2), and their average was reported as the mean F-wave latency (vertical dotted line) [9]. The distal sensory latency (DSL) was measured from stimulus onset to the initial negative peak (upward deflection) of the SNAP (open circle in the upper left panel of Figure 2). The SNAP amplitude was measured peak to peak (negative-positive, or vertical distance between open and closed circles) [10]. Both sensory parameters were based on the averaged waveform. All motor and sensory latencies were adjusted for deviation of skin surface temperature from reference values (32 °C upper extremity, 30 °C lower extremity) with a linear correction formula:  $\text{Latency}(\text{corrected}) = \text{Latency}(\text{raw}) - \text{CorrCoef} * (\text{Temperature} - \text{Reference})$ . The temperature correction factor CorrCoef was previously determined in an independent study population (150 subjects, data on file), which also found dependence of CMAP and SNAP amplitude on temperature to be not statistically significant.

### Statistical analysis

Statistical measures used to quantify NCS repeatability mirrored those used in prior studies [2, 4, 5]. The Pearson product-moment correlation (CC) was used to assess the association between NCS parameters obtained 7 days apart. Intraclass correlation coefficient (ICC) was used to determine the agreement between the two tests. Coefficient of variation (CoV) of test-retest NCS parameters was calculated and the average over all nerves was reported. Relative intertrial variation (RIV) was used to assess data variability. The RIV is the difference between two tests as a percentage of the average of the two tests [2]. Because of the small sample size, 10th and 90th percentiles of RIV were calculated for all parameters to minimize the impact of outliers. To facilitate comparison, the 5th and 95th percentile values, as reported by others [2], were also obtained for selected parameters. The mean and standard deviation of the difference between the test and retest results were also reported. Paired t-tests were carried out to ensure that two tests yielded NCS parameters with the same mean.

## RESULTS

A total of 21 healthy volunteers participated in this study. Fifteen subjects (4 females) participated in the upper

extremity repeatability study. Their ages ranged from 24 to 52 years (mean 37.1, SD 8.6 years). Height varied from 157 to 180 cm (mean 173, SD 7.9 cm). Total of 15 subjects (5 females) volunteered for the lower extremity repeatability study and nine of them had also enrolled in the upper extremity study. Their age range was 22–47 years (mean 32.6, SD 8.2 years) and height range was 157–180 cm (mean 172, SD 8.2 cm). Statistical analysis results for NCS parameters are tabulated in Table 1. The RIVs for mean FWL at 5th and 95th percentiles were [−11.4%, 9.4%], [−5.1%, 3.3%], [−4.9%, 4.5%], and [−2.8%, 4.0%], respectively, for median, ulnar, peroneal, and tibial nerves. At  $P = 0.05$  level, paired t-tests indicated that the means of all test and retest NCS parameters were the same. Pearson CCs for all latency parameters were greater than 0.80 with the exception of median nerve mean FWL (CC = 0.69). All upper extremity amplitude parameters had CCs greater than 0.85. For lower extremity nerves, repeatability measures were highest for mean FWL, followed by DML and then CMAP. All latency results were based on temperature corrected latencies. Without temperature compensation, latency parameters exhibited lower repeatability. For example, the CC values for ulnar nerve DML, mean FWL, and DSL without temperature correction were 0.72, 0.93, and 0.72, respectively. Standard deviation of the difference between test and retest results would have been 0.31, 1.04, and 0.34. No temperature correction was performed for amplitude parameters reported in Table 1.

## DISCUSSION

Several studies (summarized in Table 2) have examined NCS parameter repeatability [2, 4, 5]. In [4], the repeatability of NCS was evaluated for 60 sites participating in a clinical trial, with NCS oversight performed by “an experienced, insightful and knowledgeable core lab”. Our study yielded similar results, though our study demonstrated a higher CoV for peroneal CMAP amplitude (9% vs. 29.8%). In [2], 132 healthy subjects were retested at a time interval of 1–4 weeks and ICC and RIV were used to measure the test-retest repeatability. In comparison with that study, our study had higher ICC values for all NCS parameters except for tibial CMAP. The RIV (5th and 95th percentile) for tibial nerve F-wave latency was tighter in our study ([−2.8%, 4.0%] vs. [−4.6%, 5.7%]) while the relationship was reversed for median nerve F-wave latency results ([−11.4%, 9.4%] vs. [−6.7%, 6.7%]). Decreased repeatability of median nerve F-wave latency may be attributed to the lower amplitude signal-to-noise ratio as median nerve F-waves were acquired via a

Table 1. Statistical measures of nerve conduction study parameter repeatability

Nerve	CC	ICC	CoV	RIV Percentiles		(Day 8–Day 1)		Paired <i>t</i> -test
				10th (%)	90th (%)	Mean	Stdev	
<i>Distal motor latency (DML)</i>								
Median	0.872	0.870	0.032	-9.5	5.1	-0.055	0.194	0.289
Ulnar	0.889	0.832	0.045	-8.3	11.0	0.026	0.190	0.605
Peroneal	0.864	0.845	0.061	-15.4	8.1	-0.124	0.453	0.307
Tibial	0.850	0.824	0.038	-6.8	8.8	0.016	0.239	0.799
<i>Mean F-wave latency (FWL)</i>								
Median	0.692	0.679	0.031	-6.6	4.4	-0.037	1.970	0.943
Ulnar	0.949	0.921	0.017	-3.9	1.1	-0.286	0.915	0.246
Peroneal	0.896	0.901	0.017	-4.7	3.4	-0.163	1.563	0.693
Tibial	0.943	0.940	0.013	-1.8	3.5	0.278	1.145	0.363
<i>Distal sensory latency (DSL)</i>								
Median	0.887	0.879	0.028	-7.2	4.0	-0.056	0.189	0.270
Ulnar	0.815	0.797	0.037	-5.7	9.0	0.012	0.207	0.825
<i>Compound muscle action potential (CMAP) amplitude</i>								
Median	0.879	0.862	0.109	-19.2	19.9	0.031	0.198	0.550
Ulnar	0.981	0.974	0.045	-5.7	10.7	0.288	0.609	0.088
Peroneal	0.392	0.331	0.298	-30.8	99.5	0.849	1.937	0.112
Tibial	0.714	0.728	0.148	-30.9	25.4	-0.165	1.601	0.695
<i>Sensory nerve action potential (SNAP) amplitude</i>								
Median	0.954	0.954	0.058	-11.8	7.8	0.673	8.402	0.761
Ulnar	0.990	0.982	0.042	-4.4	10.9	1.485	5.063	0.275

CC: Pearson product moment correlation to assess the association between test-retest results. ICC: Intraclass correlation coefficient to determine the agreement between test-retest results. CoV: Coefficient of variation normalizes the standard deviation by its corresponding mean. RIV: Relative interval variation defines the difference between test-retest as a percentage of average. Paired *t*-test results indicate the means of test and retest are not statistically different. DSL is the negative peak latency and SNAP amplitude is the peak-to-peak amplitude difference. DML is the onset of initial deflection and CMAP is negative peak to baseline amplitude difference. FWL is the arithmetic mean of individual F-wave latencies in an F-wave set.

volume-conduction recording technique. Indeed, latency repeatability was much higher for ulnar F-waves recorded directly over the muscle. The ICC for ulnar F-wave latency was 0.92 in our study, higher than the ICC of 0.59 reported in a similar study of 49 healthy adults [11]. Salerno and colleagues studied upper extremity sensory test-retest repeatability based on 158 active workers who were tested by a neurologist and a physiatrist [5]. Our results fell into the upper range of their repeatability results as measured by CC and ICC.

Our study had lower CMAP amplitude repeatability than some other studies. The cause of this is uncertain. It is possible that the small recording electrodes (surface areas  $\sim 2 \text{ cm}^2$ ) used in our study degraded repeatability, since Tjon-A-Tsien and colleagues noted that when electrode size was changed from 0.78 to 7.65  $\text{cm}^2$ , the CoV of CMAP amplitude improved from 11 to 7% (lower CoV is associated with higher repeatability) [12].

DML repeatability was less affected by electrode size in both our study and the study of [12].

Skin temperature changes have a predictable effect on motor and sensory latencies [13]. However, control of skin temperature is often difficult to achieve, especially in different testing environments. In the present study, skin temperature adjacent to the recording site was acquired automatically using an embedded probe and latencies were adjusted to the reference temperature. As expected, temperature correction improved NCS repeatability. For example, the CC increased from 0.72 (without temperature correction) to 0.89 (with correction) for both motor and sensory latencies of the ulnar nerves. Temperature correction also reduced the standard deviation of the test-retest latency difference by as much as 39% (ulnar DML).

The principal limitation of the current study was the small number of subjects evaluated relative to several prior investigations. The short test-retest interval of 1 week

Table 2. Repeatability results reported in the literatures

Nerve	CC	ICC	CoV
<i>Distal motor latency (DML)</i>			
Median		0.826 <sup>a</sup>	0.04 <sup>b</sup> /0.08 <sup>c</sup>
Peroneal			0.05 <sup>b</sup> /0.08 <sup>c</sup>
Tibial		0.617 <sup>a</sup>	0.08 <sup>c</sup>
<i>Minimum F-wave latency (FWL)</i>			
Ulnar		0.59 <sup>d</sup>	
Tibial		0.921 <sup>a</sup>	
<i>Distal sensory latency (DSL)</i>			
Median	0.82–0.92 <sup>e</sup>	0.82–0.92 <sup>e</sup>	0.04 <sup>b</sup>
Ulnar	0.37–0.64 <sup>e</sup>	0.32–0.63 <sup>e</sup>	
<i>Compound muscle action potential (CMAP) amplitude</i>			
Median		0.777 <sup>a</sup>	0.07 <sup>b</sup> /0.11 <sup>c</sup>
Peroneal			0.09 <sup>b</sup>
Tibial		0.846 <sup>a</sup>	
<i>Sensory nerve action potential (SNAP) amplitude</i>			
Median	0.83–0.88 <sup>e</sup>	0.834 <sup>a</sup> /0.81–0.88 <sup>e</sup>	0.08 <sup>b</sup>
Ulnar	0.68–0.85 <sup>e</sup>	0.68–0.85 <sup>e</sup>	

<sup>a</sup> 132 healthy subjects retested in 1–4 weeks [2]. <sup>b</sup> Results for control subjects from 60 sites with core lab support in a clinical trial [4]. <sup>c</sup> 33 subjects retested in 1–2 week, results for small electrode size (0.78 cm<sup>2</sup>) and all three nerves combined [12]. <sup>d</sup> 57 healthy volunteers retested 3 days apart [11]. <sup>e</sup> 158 active workers examined by a neurologist and physiatrist on the same day [5].

reduced the likelihood of intervening physiological changes. Prior studies have shown worse repeatability for pathologic nerves. It would be valuable to quantify repeatability of the automated NCS instrument in neuropathic nerves. At the time of this study, the amplitude parameters were not compensated for temperature variation by NC-stat system. Temperature correction may improve the repeatability of the amplitude parameters, especially for sensory responses.

Repeatability was quantified for NCS parameters obtained with an automated NCS instrument. The results compared favorably with those obtained at academic and community electromyography laboratories. The reproducibility of individual NCS parameters followed the same pattern as those observed in traditional settings. F-wave latency had the greatest repeatability, followed by DML, DSL, and SNAP amplitude. The CMAP amplitude was the least reproducible parameter, with peroneal CMAP amplitude repeatability the lowest among all nerves. A larger recording electrode size should improve its repeatability. F-wave latency repeatability for median nerve was lower due to the lower signal-to-noise ratio inherent in volume-conduction recordings. As a result,

over-muscle recording would be expected to enhance F-wave repeatability, which was the case for the ulnar nerve. Further studies with longer test-retest intervals and a higher subject count would be valuable in confirming the high reproducibility of NCS parameters measured in this study. Extending the study to pathologic nerves and validating the equivalent or superior performance of automated NCS instrument should increase the adoption rate of the automated NCS technology in patient management.

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