FINAL PROGRESS REPORT

Title page

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List of terms and abbreviations

CTS	Carpal tunnel syndrome
MMN	Median mononeuropathy
MSD	Musculoskeletal disorder(s)
NIOSH	National Institute for Occupational Safety and Health
NCV	Nerve conduction velocity
NSAIDs	Non-steroidal anti-inflammatory drugs (such as ibuprofen, Medicam, etc.)
WMSD	Work-related musculoskeletal disorder(s)

Title: Macaque Model of Carpal Tunnel Syndrome: Effects of Force and Posture Exposures
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Abstract (word count: 500)

"The role of overuse of the hand…in causation of carpal tunnel syndrome (CTS) remains controversial…" (Bland, 2005). Many epidemiological studies have been conducted to determine if CTS is a work-related disorder, and if so, what risk factors contribute to its development. Evidence exists for and against CTS as a work-related disorder, in particular, because there are several non-occupational risk factors associated with CTS. Animal models offer several advantages in the study of CTS, including ability to directly explore physical exposure and health outcomes as they develop over time. Another is elimination or control of many personal factors associated with CTS, Our preliminary research, employing our unique animal model of CTS, demonstrated a causal connection between exposure to moderately forceful, repetitive manual work and development of median mononeuropathy at the wrist (analogous to CTS in humans) (Sommerich et al., 2007). Our results further substantiated the pattern of evidence provided through prior epidemiological and laboratory-based studies. In the current study we proposed to investigate outcomes from exposure to different levels of two risk factors (posture and force) identified in epidemiological or laboratory research as important or biomechanically-relevant to development of CTS in humans (Phase 1: aims 1 and 2), and to expand our database of maximum voluntary pinch force of macaques (Phase 2: aim 3), the latter is relevant to setting experimental force levels (as % of maximum). In Phase 1, twenty-four macaques performed a repetitive, slightly or moderately forceful pinch task for food rewards for 18 weeks. They performed the task in one of three work postures: wrist flexion, neutral, or extension. Nerve conduction velocity (NCV) was the primary dependent measure. Key findings: 1) a declining trend in NCV was observed in two-thirds of the animals, 2) only animals who worked in flexion developed a pronounced and protracted decline in NCV, 3) only a small percentage (3 of 17) animals who worked at a force level near or above 20% of their predicted maximum showed no evidence of decline in NCV, 4) a moderate association (correlation) was found across subjects between decline in NCV and repetition, 5) moderate to strong associations were found between NCV and pinch force, repetition, and work measure variables for animals that showed extended declines in NCV. In Phase 2, strength data were obtained from 17 subjects, using a custom-designed apparatus built to assess maximal pinch force in neutral, flexed, and extended wrist postures. Key findings: 1) pinch strength declined from neutral to flexed to extended postures, 2) correlations were strongest between wrist circumference and peak pinch strength for neutral and extended postures, 3) in flexed posture, body mass showed a stronger correlation with pinch strength than did wrist circumference. Overall, study results are consistent with findings from our previous study and other animal models that demonstrate that moderately forceful, repetitive use of the end effector of the upper extremity can have detrimental effects on elements of the musculoskeletal system, including the median nerve, which supports the concept of CTS as a work-related disorder in some workers.

1. Significant findings

Specific Aim 1. To quantify the effects of force and wrist posture in altering the expected development of CTS.

> Significant Findings: 1) a declining trend in nerve conduction velocity (NCV) was observed in two-thirds of the animals, 2) only animals who worked in flexion developed a pronounced and protracted decline in NCV, 3) only a small percentage (3 of 17) animals who worked at a force level near or above 20% of their predicted maximum showed no evidence of decline in NCV, 4) a moderate association (correlation) was found across subjects between decline in NCV and repetition, 5) moderate to strong associations were found between NCV and pinch force, repetition, and work measure variables for animals that showed extended declines in NCV.

Specific Aim 2. To quantify the recovery period associated with a natural recovery from CTS

> Significant Findings: All subjects who displayed a reduction in NCV also displayed recovery to baseline within the timeframe of the study. Only two periods of recovery (two subjects) occurred after work exposure was concluded, which was unexpected and is discussed in the body of the report. The rate of recovery of one subject was, 1.6% per week, was similar to rates seen in our previous R21 study that employed the macaque model. The rate for the other subject was about 3% per week, and may have been affected by administration of NSAIDs.

Specific Aim 3. To expand our database of maximum voluntary pinch exertion force of the macaque, which we use to predict and set experimental levels of force (as % of maximum) in our protocols.

> Significant Findings: 1) pinch strength declined from neutral to flexed to extended postures, 2) correlations were strongest between wrist circumference and peak pinch strength for neutral and extended postures, 3) in flexed posture, body mass showed a stronger correlation with pinch strength than did wrist circumference.

2. Translation of findings

Overall, study results are consistent with findings from our previous study and other animal models that demonstrate that moderately forceful, repetitive use of the end effector of the upper extremity can have detrimental effects on elements of the musculoskeletal system, including the median nerve. These findings are consistent with two important reviews of the epidemiological literature on CTS in work populations, and supports the concept of CTS as a work-related disorder in some workers. The results from the current study could be used to guide future investigative or intervention activities, involving this animal model and studies in humans. Results from this study continue to support the value of the macaque model for studying effects on NCV of differences in hand configuration in task performance, as an additional means of providing an intervention. In the current study, biweekly nerve health monitoring was, again, demonstrated to effectively detect and document decline in nerve health. Biweekly nerve health monitoring in human working populations, wherein work may be suspected of contributing to development of carpal tunnel syndrome, is becoming more feasible with alternative methods that are proving to be sensitive and specific, such as use of sonography, but do not cause discomfort during testing, as does nerve conduction testing.

3. Outcomes / Impact

As in the prior R21 study, the current study demonstrated a temporally unambiguous relationship between a moderately forceful, repetitive pinching task and development of median mononeuropathy, as defined by a decline in nerve conduction velocity (NCV) over several weeks. The development of median mononeuropathy in the subjects again demonstrates that a combination of a moderate level of force, pinch gripping, wrist flexion, and brief finite hold duration, without exposure to vibration or cold, can lead to significant reduction in NCV in subjects with normal nerve conduction prior to task exposure. These results are consistent with results from other animal models and with reviews in the epidemiological literature that identify awkward wrist postures and moderately forceful, repetitive pinching to be risk factors for carpal tunnel syndrome. Engineers, occupational safety professionals, and others responsible for work task design elements should check for these risk factors when they perform job safety analyses or other hazard analyses at their work sites.

4. Scientific Report

4.1 Background for the project

Carpal tunnel syndrome is thought to result from localized compression of the median nerve within the carpal tunnel and is the most commonly encountered peripheral neuropathy (Falkiner & Myers, 2002; Werner & Andary, 2002). Incidence rates for women are often reported to be greater than for men (Franklin, Haug, Heyer, Checkoway, & Peck, 1991; Hennessey & Johnson, 1997). Occurrence of CTS in workers has been shown to differ considerably between hand-use-intensive jobs and other types of jobs. The median number of lost work days per CTS case, typically 25-28 days, is about four times that of the median number of lost days across all lost time injuries and illnesses (6-7 days). This makes CTS comparable to back pain on the basis of annual lost work days. Katz et al. (2005) found that about 20% of a sample of workers who had CTS release surgery were not working at survey points of 6 and 12 months after surgery, as well as prior to the surgery (about one-half of those off work at each point in time were not off work at the other points in time).

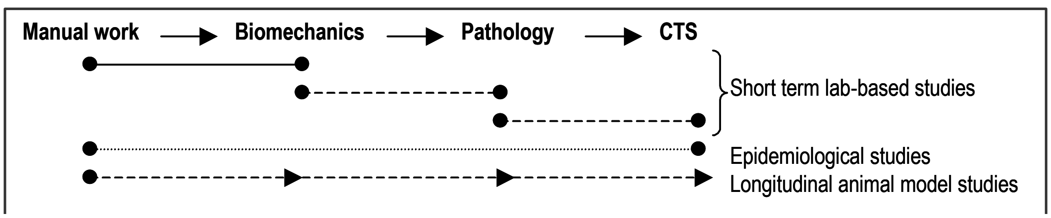


Fig. 4.1 Most study designs do not permit exploring the full connection between manual work and CTS development. Animal models provide the opportunity to explore the effects of exposure over time.

"The role of overuse of the hand…in causation of CTS remains controversial…" (Bland, 2005). Many epidemiological studies have been conducted to determine whether or not CTS is a work-related disorder, and if so, what risk factors contribute to its development. Evidence exists for and against CTS as a work-related disorder, in particular, because there are several non-occupational risk factors associated with CTS. Both work factors and non-work factors have also been associated with extended work absence (6 months) following surgical intervention for CTS (Katz et al., 2005). An alternative way of demonstrating an association between work factors and CTS would be to show that changes (interventions) to certain aspects of work had the effect of reducing or preventing CTS. However, a review of two dozen intervention studies concluded that "none of the studies conclusively demonstrates that the interventions would result in the primary prevention of carpal tunnel syndrome in a working population" (Lincoln et al., 2000). The review indicated that many of the studies had methodological problems, including not measuring impact on CTS occurrence or not controlling for important confounding factors. There is also limited research, in terms of controlled trials, into efficacy of medical (non-surgical) interventions or interventions that combine medical and workplace approaches (Bland, 2005; Verdugo, Salinas, Castillo, & Cea, 2003). The ability to control confounding factors associated with CTS is critical to determining if certain physical factors are important risk factors for CTS or if certain levels of those factors reduce the risk of CTS.

Animal models offer several advantages in the study of CTS, including the ability to directly explore physical exposure and health outcomes (Fig. 4.1). Another is elimination or control of most of the personal factors that have been associated with CTS, including gender, age, obesity, reduced fitness, smoking, alcohol use, caffeine use, diabetes, renal disease, thyroid disease, pregnancy, lactation, and sports participation (Falkiner & Myers, 2002). Use of validated animal models provides the opportunity to characterize dose-response relationships between risk factors (separately and in combinations) and CTS. Animal models can also allow for the study of various treatment interventions and study of work regimens following intervention. Much new, important work has been published in this area since the current study was proposed, primarily by Barbe and Barr and colleagues, including examining changes in the brain as an outcome of exposure to repetitive manual tasks; their body of work will be addressed in the discussion section of this report (Coq et al., 2009; Driban, Barr, Amin, Sitler, & Barbe, 2011; Elliott et al., 2009; Elliott et al., 2008; Fedorczyk et al., 2010; Kietrys, Barr, & Barbe, 2011).

4.2 Specific aims

The long term goal of the line of work to which the current study belongs is prevention of work-related carpal tunnel syndrome (CTS). At the time the study was proposed there was limited knowledge of the effects of different exposure conditions to occupational risk factors associated with CTS. In working populations, it is difficult to study the development of the CTS, partly because there are a number of systemic, genetic, and other health conditions that have been associated with CTS. Controlled investigations of exposure-response relationships using animal models were still fairly rare at the time the current study was proposed. The value of animal models, as has been seen over the last several years, is that they can elucidate a host of outcomes that can be directly and causally associated with specific exposure phenomena (Al-Shatti, Barr, Safadi, Amin, & Barbe, 2005; Barr et al., 2003; Carp, Barbe, Winter, Amin, & Barr, 2007; Clark, Al-Shatti, Barr, Amin, & Barbe, 2004; Clark et al., 2003; Coq et al., 2009; Elliott et al., 2009). Additionally animal studies have begun to facilitate the study of interventions that will translate to effective workplace interventions that could be used to prevent or possibly facilitate the recovery from CTS (Driban et al., 2011; Kietrys et al., 2011).

As originally proposed, the primary goal of the current study was to quantify the effects of exposure to different levels of hand force and wrist posture on the development of median mononeuropathy at the wrist (carpal tunnel syndrome, CTS). Much of what is known about CTS etiology is based on epidemiological and controlled laboratory investigations. Several occupational risk factors have been identified that "provide evidence of causation" (Bernard, 1997) in the development or exacerbation of CTS, including highly repetitive or forceful work (Bernard, 1997; Viikari-Juntura & Silverstein, 1999) and extreme postures (Viikari-Juntura & Silverstein, 1999). Bernard (1997) also found "strong evidence" of an association between CTS and combinations of risk factors. Alone, epidemiological evidence associating physical risk factors with CTS is compelling. However, it is difficult to study exposure-response relationships between risk factors and CTS and draw unequivocal conclusions about those relationships, because exposure to some risk factors cannot always be adequately measured, nor all the other (personal) risk factors that are also associated with CTS controlled in such studies. Further, prospective studies in human populations, which ensure the correct temporal aspect of the relationship, are expensive and very challenging to conduct. Most epidemiological studies of CTS, have, in fact, been cross-sectional or retrospective in design, and each of those designs has some limitations when it comes to investigating causal associations between work and CTS. This explains the need for complementary, controlled, experimental research into CTS etiology. Our preliminary research, employing our unique animal model of CTS, demonstrated a causal connection between exposure to moderately forceful, repetitive manual work and development of median mononeuropathy at the wrist (analogous to CTS in humans) (Sommerich et al., 2007). Our results further substantiated the pattern of evidence provided through prior epidemiological and laboratory-based studies.

Others had developed methods to study nerve entrapment in animals models at the time the current study was proposed: the rat (Clark et al., 2004; Clark et al., 2003; Mackinnon, Dellon, Hudson, & Hunter, 1984) and the rabbit (Rempel, King, Robertson, Dahlin, & Abrahmsson, 2001) were being or had been studied. These models were very useful for understanding biochemical and histological responses. Previous relevant use of non-human primates was limited to insertion of a restriction around the median nerve (Mackinnon & Dellon, 1988; Mackinnon, Dellon, Hudson, & Hunter, 1985) in order to study surgical repair methods, and studies of acute compression (Schneider & Dellon, 1983) and focal dystonia and changes in the brain (Topp & Byl, 1999). At the time the current study was proposed we were able to say that our animal model was a significant development, because 1) the anatomy of the monkey's hand is very similar to humans', 2) the monkey's typical use of the hand is similar to humans', 3) the work task (repetitive, moderately forceful pinching task) is performed voluntarily, 4) the work task closely resembles work performed by human hands in occupational settings, 5) the model affords study of various hand tasks, 6) CTS onset, recovery, and recurrence can be studied longitudinally, 7) development of symptoms over a 2 – 4 month timeframe is biologically plausible as a model of chronic changes associated with CTS, and 8) no invasive methods are used, so all changes to the nerve can be attributed to the experimental (task) exposure. One advantage this model maintains over a rat model is the ability to configure the hand and wrist in ways that are most similar to human hand configurations. However, other elements of the monkey model are shared with Barbe and Barr's rat model (Barbe et al., 2003; Barr et al., 2003; Elliott et al., 2009; Elliott et al., 2008). Additionally, the rat model offers some important advantages over a monkey model. This will be discussed later in this report.

In the current study we proposed to systematically investigate outcomes from exposure to different levels of two risk factors identified in epidemiological or laboratory research as important or biomechanically-relevant to development of CTS in humans. We also proposed to begin to study potential workplace interventions for preventing development of CTS, by contrasting lower and higher levels of these factors.

The specific aims of the current study were:

1. To quantify the effects of force and wrist posture in altering the expected development of CTS;
2. To quantify the recovery period associated with a natural recovery from CTS; and
3. To expand our database of maximum voluntary pinch exertion force of the macaque, which we use to predict and set experimental levels of force (as % of maximum) in our protocols.

4.3 Phases 1 & 2

Aim 1. To quantify the effects of force and wrist posture in altering the expected development of CTS.
Aim 2. To quantify the recovery period associated with a natural recovery from CTS

4.3.1 Background

Extensive reviews of the epidemiological literature suggest that work is associated CTS. Bernard (1997) reviewed over 30 epidemiological studies of workplace factors and CTS and determined that there was "strong evidence" of a positive association between combinations of risk factors and CTS; that there was "evidence" of a positive association between CTS and highly repetitive work alone or in combination with other factors (including posture); and that there was "evidence" of a positive association between forceful work and CTS. They did not find sufficient evidence of an association between CTS and extreme postures, alone. In their review of 38 studies, Palmer et al. (2007) concluded that there was elevated risk from prolonged and highly repetitious flexion and extension of the wrist, especially when allied with a forceful grip". Viikari-Juntura and Silverstein (1999) examined the pattern of evidence of the role of "modifiable workplace physical factors" in the development of CTS, by reviewing studies from many areas – epidemiological, experimental, cadaver, and animal. One of the consistent and unifying threads they found was the connection of the external, physical factors (posture, force, repetition, and external pressure) to carpal tunnel pressure (CTP; the pressure that is measured within the carpal tunnel). They concluded that there is sufficient evidence that duration, frequency, or intensity of exposure to forceful repetitive work and extreme wrist postures is likely to be related to the occurrence of CTS in working populations.

However, in working populations, it is difficult to study the <u>development</u> of the CTS, partly because there are a number of systemic, genetic, and other health conditions that have been associated with CTS. Controlled investigations of exposure-response relationships using animal models were still fairly rare at the time the current study was proposed. The value of animal models, as has been seen over the last several years, is that they can elucidate a host of outcomes that can be directly and causally associated with specific exposure phenomena (Al-Shatti et al., 2005; Barr et al., 2003; Carp et al., 2007; Clark et al., 2004; Clark et al., 2003; Coq et al., 2009; Elliott et al., 2009). The first two aims of the current study were to take a more detailed and systematic look at the effects of wrist posture and pinch force on nerve conduction velocity (aim 1) and to quantify the recovery period associated with a natural recovery from CTS (aim 2).

4.3.2 Methodology

Exposure: pinch task and apparatus. Subjects performed a repetitive pinching task that was available to them 6 hours per day, 5 days per week. Element of the task were based closely on the task used in our previous R21 study (Sommerich et al., 2007), which in turn, was based on factors identified in a CTS case-referent study by Roquelaure et al. (1997). A pinch task apparatus was clamped to each subject's cage every morning and removed every evening (Fig. 4.2 & 4.3). The exception to this routine occurred on the day of the bi-weekly (every other week) nerve conduction testing. In total, subjects typically worked 9 days of every two week cycle during the work phase of the study.

The study design was a between-subjects design that would provide for exposure of sets of four subjects to one of six pinch force (10% and 20% MVC) and wrist posture (flexed, neutral, and extended) combinations. The planned schedule for the exposures was:

- Yr 1: 4 subjects working in flexion at 20% calculated MVE pinch and 4 subjects working in neutral position at 20% MVE
- Yr 2: 4 subjects working in extension at 20% MVE pinch and 4 subjects working in neutral position at 10% MVE
- Yr 3: 4 subjects working in flexion at 10% MVE pinch and 4 subjects working in extension at 20% MVE.

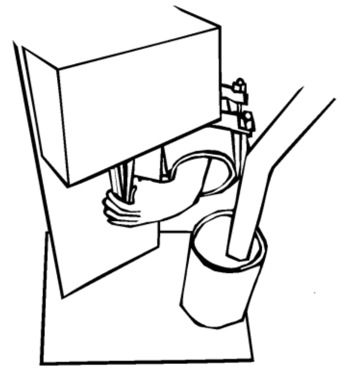


Fig. 4.2 Illustration of task performed with flexed write. Bird's eye view of the pinching apparatus mounted on cage, with monkey's hand projecting out the end of the tube with wrist flexed and fingers pinching the two levers of the apparatus.

A new pinch apparatus was designed for this study (Fig. 4.3). The apparatus can be oriented to allow/restrict subjects to work with the wrist in a flexed, neutral, or extended posture. The new device allowed us to measure force (via strain gages) directly and independently for each tong, as well as measure directly and independently movement of each tong. Tong movement was measured with an optical sensor; the device we designed for the previous R21 study used a rotary potentiometer that measured only the combined motion of the two tongs, and did not measure force. The main advantage of the optical sensors is a design that provides movement information independently for each tong. These improvements allow the examination of individual technique of each subject, and possibly help us understand different rates of neuropathy development or outcome.

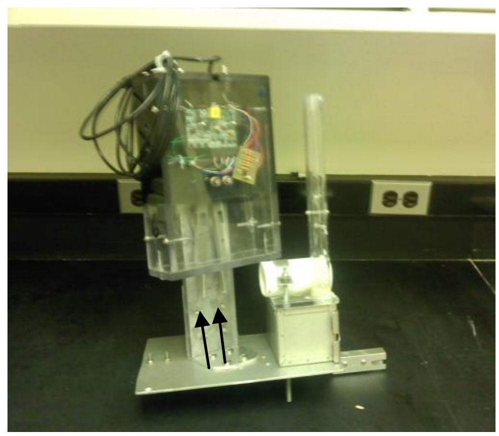


Fig. 4.3 Photograph of pinch apparatus developed for this study. Each arrow points to the end of one tong.

Data collection hardware and software were redeveloped for this study. The system controlled the task for 8 subjects at a time, recorded and categorized pinch responses (as attempts, pinches, or successes), and recorded strain gage and optical sensor data for each tong on each device. Pictured in Fig. 4.4 is the room where the subjects worked. In the center of the picture is the computer that controlled the task for each pinch apparatus and that collected performance data. On either side of the computer are four cages with one pinch apparatus attached on the front of each cage. The room was set-up in this fashion for 6 hours/day during week days for the subjects to work on the

Fig. 4.4 Cages with apparatus mounted on the front; computer that runs the task and acquires the performance data is located in the center of the room.

task. A script was written using Spike2 software (CED, Cambridge, England), to process the sensor and strain gage data. Task data were reduced to the variables listed in Table 4.1, for analysis and reporting purposes. Variables were calculated on a two week basis, in order to correspond with nerve conduction testing values.   The exposure variables were also calculated on an average daily basis within each two-week period.

Table 4.1 Exposure variables presented in this report.

Variable	**Definition**
Repetitions were categorized as a success, pinch, or attempt	• Success – force, closure distance, and duration all meet criteria and the effort was rewarded with a food pellet. • Pinch – sufficient force and closure distance; includes successes and efforts not held long enough to be rewarded. • Attempt – any effort of tong displacement that exceeded the closure threshold (10%); pinches are a subset of attempts.
Work-time	The product of the sum of the pinch force exerted on each tong multiplied by the displacement distance of each tong multiplied by the time of the exertion. Units are kN-m-s
Efficiency	(Attempts – successes)/successes; reflects task learning
Success/attempt ratio	Successes/attempts; another way of characterizing task learning

Exposure timeframe. Subjects were to be exposed to the pinching task until either 1) achieving at least a 25% decline in NCV in two successive biweekly nerve conduction studies, or 2) task exposure duration has reached 18 weeks (based on the longest time to develop CTS in our previous R21 study in which this animal model was developed), or 3) subject is unable or unwilling to work after being treated via the NSAIDs treatment protocol and/or re-evaluating our behavioral shaping efforts with the individual.

Assessment – nerve conduction testing. The setup for NCV testing is illustrated in Fig 4.5 Ring electrodes were placed over digits 2 and 5. Surface EMG electrodes were placed over the thenar and hypothenar eminences. Stimulation was applied through a bipolar electrode placed over the nerve of interest (median or ulnar) 6.0 cm away from the proximal ring electrode. Testing was performed under Isoflorane anesthesia so there was no movement or background EMG to contaminate the baseline. The latency of the sensory nerve action potential's (SNAP's) take-off and peak depolarization were measured from the averaged response to a set of five stimuli at the selected test current (Fig 4.3A). Custom-developed software automatically identified take-off, first negative peak, peak-peak amplitude, and produced a report at the conclusion of the testing session. Calculation of NCV required identification of an appropriate test current for each testing session, based on the recruitment curves for the sensory nerve action potentials (SNAPs) and compound motor action potentials (CMAPs). Custom software produced these recruitment curves by applying stimulation at selected intensities between subthreshold and supramaximal in randomly ordered sets of all intensities until 5 stimuli were delivered at each

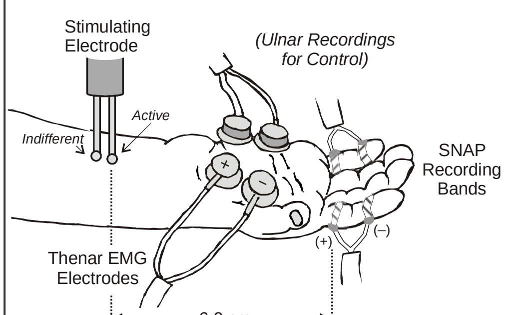


Fig. 4.5 Setup for electrodiagnostic testing.

intensitiy. The software automatically plotted stimulus current versus peak-to-peak amplitude of SNAP and CMAP (Fig. 4.6B). From this recruitment curve, the currents that produce maximal amplitudes of the SNAP and CMAP were identified. The test current is the stimulus intensity that evokes a maximal SNAP, which is typically about 1.1 times the current required for a maximal CMAP (Adour, Sheldon, & Kahn, 1977).

NCVs were calculated from take-off and peak latencies (Fig 4.6 A). Peak latencies are most stable across sessions, but take-off latencies may be most sensitive to early impairment, so both were used. CMAPs were used to make recruitment curves (Fig 4.6 B) and to verify that median nerve stimulation did not produce hypothenar EMG responses (and vice versa for ulnar nerve stimulation).

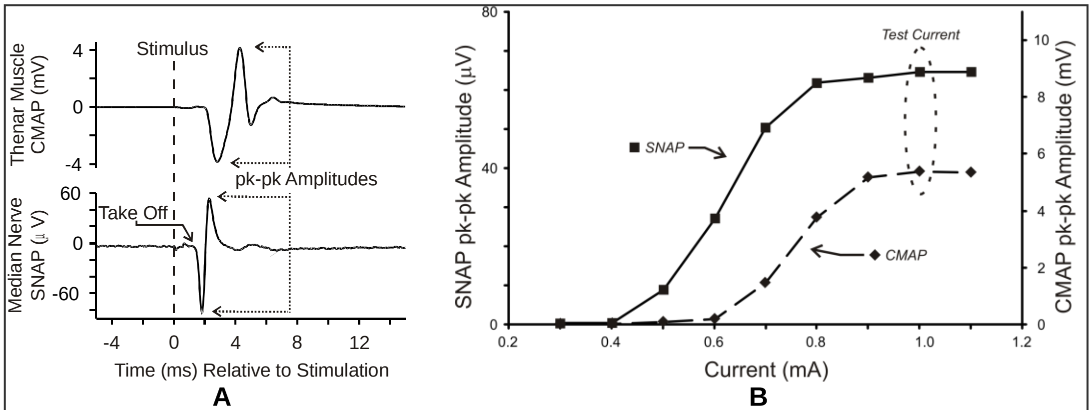


Fig. 4.6 **A**. Sample sensory (SNAP) and compound motor action potentials (CMAP). **B.** Amplitude of sensory and motor action potentials as a function of stimulation current. Circled point shows selected test current.

4.3.3 Results and discussion

A declining trend in nerve conduction velocity was observed in two-thirds of the animals. Table 4.2 provides a summary of the outcomes, along with test condition categories and exposure conditions.

Table 4.2 Test conditions and categorical outcomes for each animal. Cohorts are separated by the bold horizontal line. Green, yellow, and gray shading duplicates column 3 categorizations by exposure category.

Subject	wrist posture	Qualitative assessment of effect on NCV (n=no, s=some, y=yes)	tong force measured, N	20% of strength from wrist equation using trend line	spring force as % of calculated strength, based on equation	Flex 10%	Flex 20%	Neut 10%	Neut 20%	Exten 10%	Exten 20%	
A	N	S	4.9	4.1	23.9%				1			
B	F	S	6.5	6.5	20.0%		1					
C	N	N	7.1	6.8	20.9%				1			
D[**b]	N	S	7.1	7.4	19.2%				1			
E	F	Y	7.4	6.8	21.8%		1					
F[**a]	F	Y	9.1	8.1	22.5%		1					
H	F	Y	10.6	9.1	23.3%		1					
L	N	S	7.4	7.8	19.0%				1			21%
I	F	N	7.6	9.7	15.7%		1					
J[**b]	E	N	3.7	7.1	10.4%					1		
K	F	N	5.9	8.1	14.6%	1						
M	F	Y	6.4	9.7	13.2%	1						
N	E	S	8	9.7	16.5%						1	
O	E	N	6.9	9.7	14.2%					1		
Q[**b]	F	S	6.4	8.4	15.2%		1					14%
R[**b]	F	S	5.5	8.4	13.1%	1						
S[**b]	F	N	10.8	8.4	25.7%		1					
T	F	Y	12.6	6.8	37.1%		1					
U	F	S	9.5	8.7	21.8%		1					
W	F	Y	8.6	6.5	26.5%		1					
X	F	Y	6.7	7.8	17.2%		1					
Y	F	Y	11.2	7.7	29.1%		1					24%

Distribution of outcomes within exposure categories:	NCV effect	Flex 10%	Flex 20%	Neut 10%	Neut 20%	Exten 10%	Exten 20%
	n	0.33	0.17		0.25	1.00	
	s	0.33	0.25		0.75		1.00
	y	0.33	0.58				
	totals	3	12	0	4	2	1

Notes for Table 4.2:
** Removed from task early: a = unrelated injury, b = stopped working

As can be seen from Table 4.2, beyond the first year's testing (that is, for subjects I - Y) there was some deviation from the planned testing conditions, in terms of force and posture conditions. There were some important reasons for this, including some concerns over the applicability of the original equation for setting force level exposure and the outcomes from year 1 testing to the second cohort. Due to the equivocal results of the neutral and extension exposures at either level of force, we had concerns about explicitly trying to set-up 10% force testing conditions in the neutral posture, and we had concerns about attempting to achieve 20% in extension, when that had not been successful in year 2. As can be seen in the table, forces for cohort 2 were lower than for the other two cohorts in order to persuade them to perform the task. In the end, most of the subjects were tested in flexion, and the study devolved into a series of case studies, though some summary conclusions can be made about the results:

- Only animals who worked in flexion developed a pronounced and protracted decline in the NCV in the working hand.
- Only a small percentage (3 of 17) animals who worked at a force level near or above 20% of their predicted maximum showed no evidence of a decline in NCV in the working hand.

Work exposure data are provided in Table 4.3. The table provides the sum total exposure of each animal, in terms of pinch counts (success and attempt; pinch data are not provided because the counts are very close to the attempt counts for each animal) and work-time. The table also provides daily average values of these same measures. As a point of reference, a maximum of approximately 2160 attempts was possible in a given day (= maximum of 6 pinches per minute X 60 min/hr X 6 hr).

Table 4.3 Exposure summary and reduction in NCV. Row shading classifies by effects on NCV: Y = darker shading, S = lighter shading, N = no shading.

Subject	wrist posture	Maximum NCV decline from baseline, %	tong force measured, N	20% of strength from wrist equation using trend line	spring force as % of calculated strength, based on equation	Cumulative total exposure			Average daily			
						success	attempt	work-time, kN-m-s	success	attempt	work-time, kN-m-s	Learning rate, %
A	N	16	4.9	4.1	23.9	66,022	79,166	68.6	690	861	0.73	42
B	F	22	6.5	6.5	20.0	142,214	158,172	114.2	1395	1625	1.26	54
C	N	-	7.1	6.8	20.9	99,800	109,275	137.9	1193	1291	1.63	60
D**b	N	11	7.1	7.4	19.2	84,889	99,374	95.6	1146	1326	1.29	64
E	F	24	7.4	6.8	21.8	77,953	110,938	112.8	974	1319	1.37	40
F**a	F	26	9.1	8.1	22.5	20,909	35,005	32.9	684	1155	1.11	x
H	F	17	10.6	9.1	23.3	112,979	125,772	245.2	1128	1259	2.56	55
L	N	20	7.4	7.8	19.0	77,630	97,479	119.0	923	1132	1.39	47
I	F	-	7.6	9.7	15.7	49,343	71,568	na*	629	913	na*	80
J**b	E	-	3.7	7.1	10.4	14,207	29,009	na*	188	393	na*	-**
K	F	-	5.9	8.1	14.6	54,037	108,029	na*	714	1429	na*	-*
M	F	22	6.4	9.7	13.2	53,303	73,945	na*	848	1136	na*	62
N	E	9	8	9.7	16.5	56,861	69,932	na*	781	952	na*	58
O	E	-	6.9	9.7	14.2	60,688	121,626	na*	893	1786	na*	-*
Q**b	F	12	6.4	8.4	15.2	14,780	23,912	na*	204	348	na*	-*
R**b	F	5	5.5	8.4	13.1	20,214	30,992	37.6	429	675	0.69	67
S**b	F	-	10.8	8.4	25.7	62,969	78,499	146.1	857	1067	1.99	83
T	F	17	12.6	6.8	37.1	76,959	116,996	217.6	862	1216	2.52	55
U	F	15	9.5	8.7	21.8	31,708	50,797	83.6	433	688	1.13	-*
W	F	18	8.6	6.5	26.5	61,566	87,077	104.5	665	940	1.18	56
X	F	12	6.7	7.8	17.2	63,661	90,979	74.8	788	1059	0.92	56
Y	F	15	11.2	7.7	29.1	75,571	104,535	166.2	762	1037	1.75	67

Notes for Table 4.3:

* na – not available; some problems were encountered with analysis and storage of some of the data prevented us from being able to provide this analysis for these animals.

** Removed from task early: a = unrelated injury, b = stopped working

x too few data points to determine rate

-* no “learning curve” evident

-** “learning” is not readily or adequately quantified by a constant rate (power equation)

Worth noting in Table 4.3 are the following:

- Five of 7 subjects who did not display a learning curve (no improvement in narrowing the difference between attempts and successes) or whose rate was very high (means a shallow learning curve that does not show much change/improvement) did not experience a change in NCV. Another way to look at this is to consider that 6 of 7 subjects who did not show a declining trend in NCV did not display a learning curve or their rate was very high (meaning not much change is displayed from one data point to the next).
- There does not appear to be a pattern with regards to total work exposure and effect on NCV across subjects. However, there is a modest relationship (r=0.55) between average daily attempts and maximum percentage decline in NCV, for subjects that experienced a decline in NCV (Figure 4.7). The relationship is weaker for successes (r=0.40), and there is no relationship across subjects for average daily work-time[1].

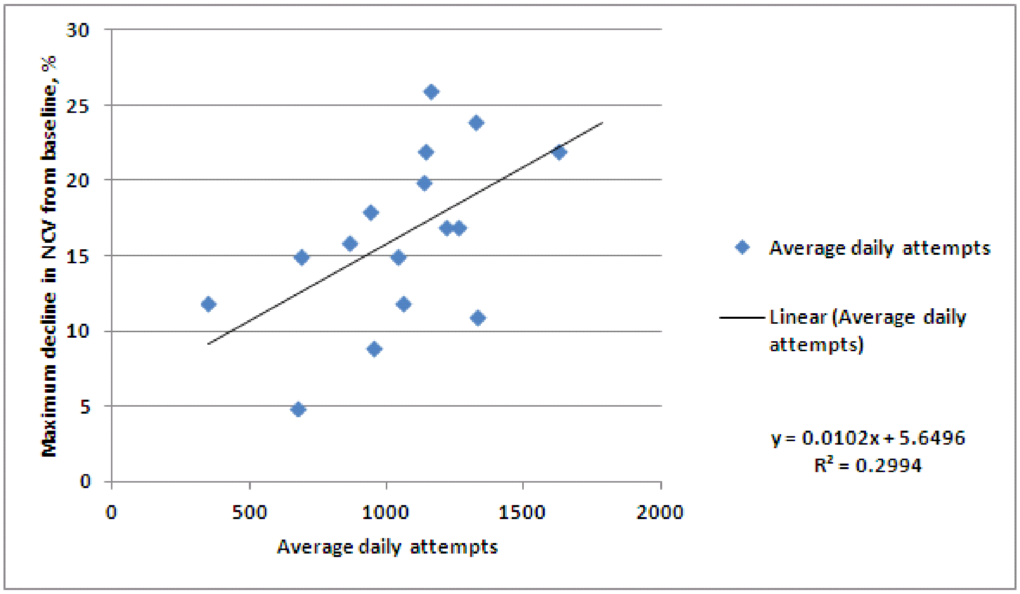


Fig. 4.7 Association between maximum NCV decline and average daily pinch attempts. Correlation (r) is 0.55.

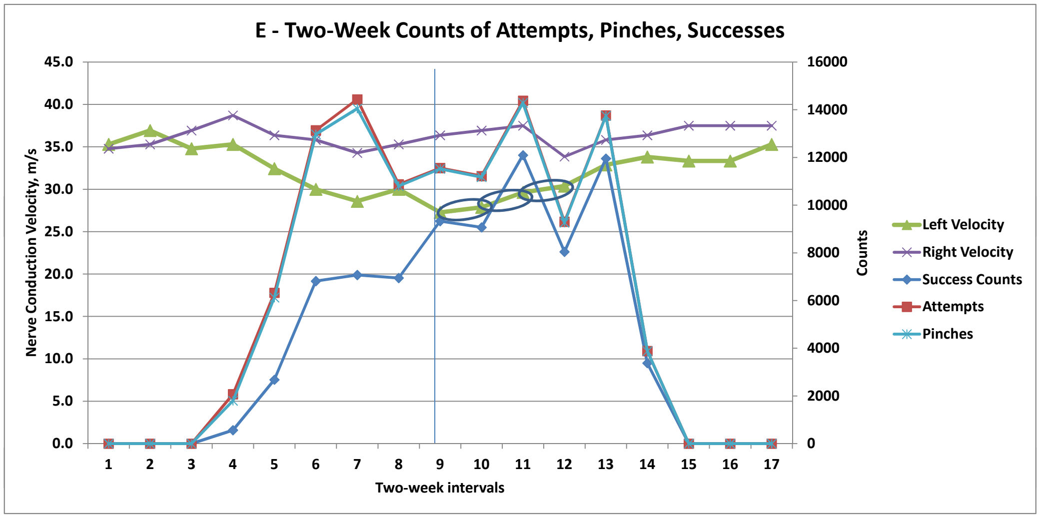
The next several pages contain “case study” results, by subject. A page of results is provided for each subject that showed a strong effect (‘Y’ category in Table 4.2); while some examples are provided for those who showed some modest effects in NCV (‘S’ category) or no effects (‘N’ category). Each page contains graphs that depict NCV, exposure assessments (counts and work measurement), and learning assessments.

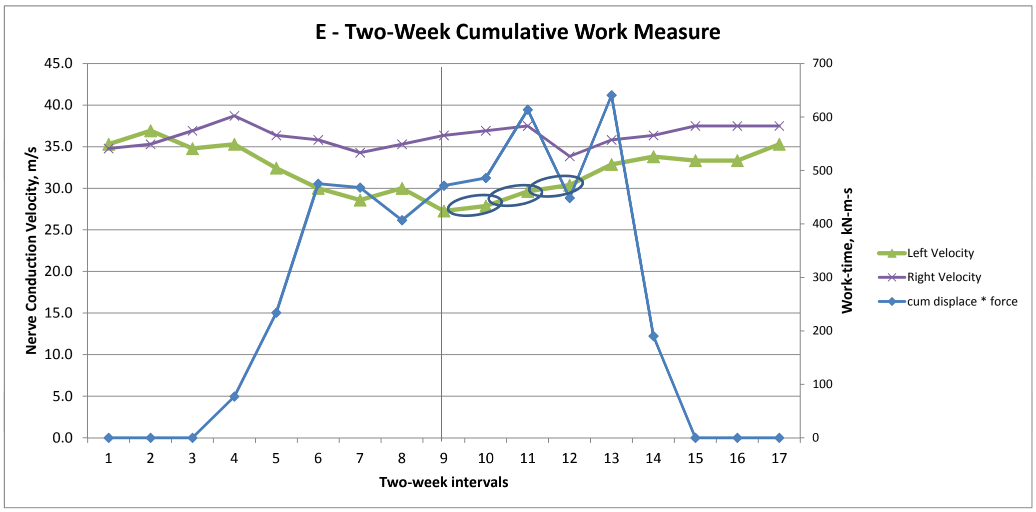
[1] We were not fully able to explore an association between work-time and NCV because there were problems with accessing portions of the data needed to make those calculations for the second cohort. Those animals worked at a lower force level and also displayed less effect on NCV than the other two cohorts. Further investigation would be needed to resolve this question.

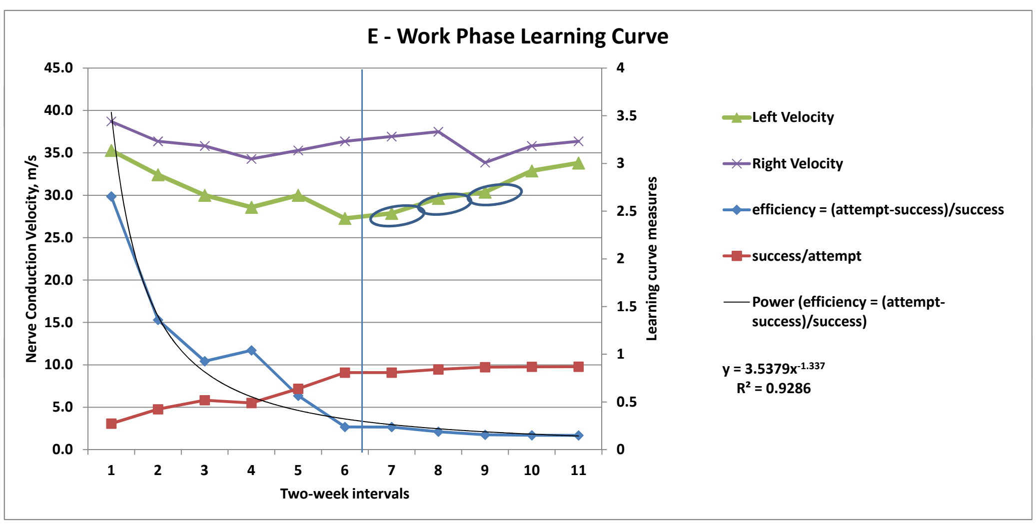
Following this page, in the PDF version of this report, there is an insertion of 8 unnumbered pages that contains exposure-response graphs for subjects that demonstrated a sustained decline in NCV while performing the pinch task.

In order, they are E, F, H, M, T, W, X, Y.

Vertical lines are provided in the graphs, on a given page, in order to help the reader match observations (data points) across graphs.





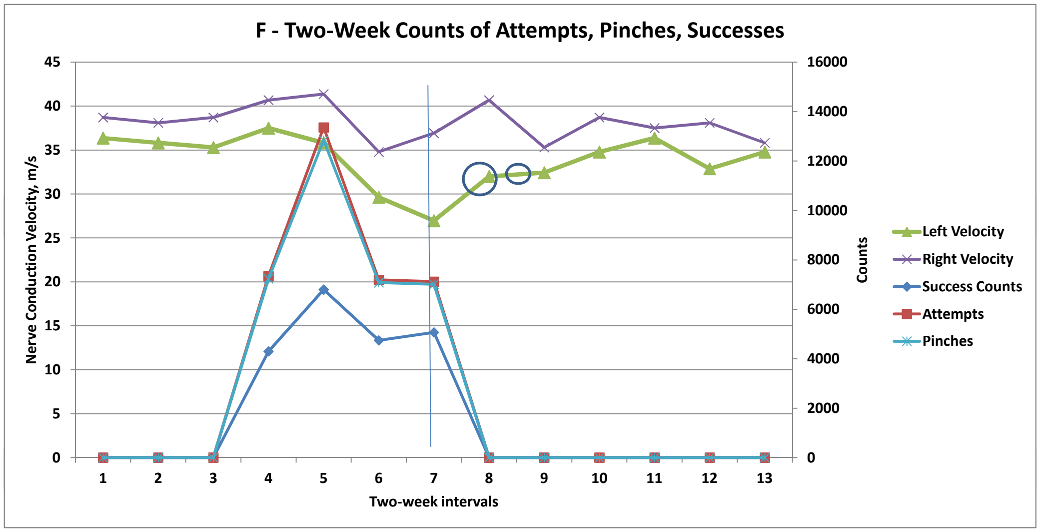


NOTES:

Steady decline in NCV with commencement of work.

NCV begins to recover during work phase, after learning curve remission and flattening of curve.

Recovery may have been influenced by administration of NSAID (circled points) for issue unrelated to work task.

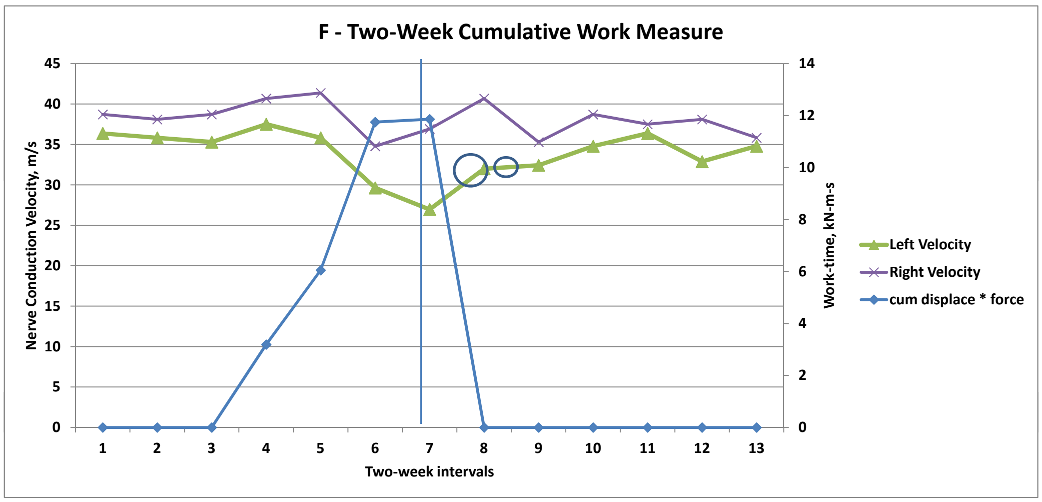


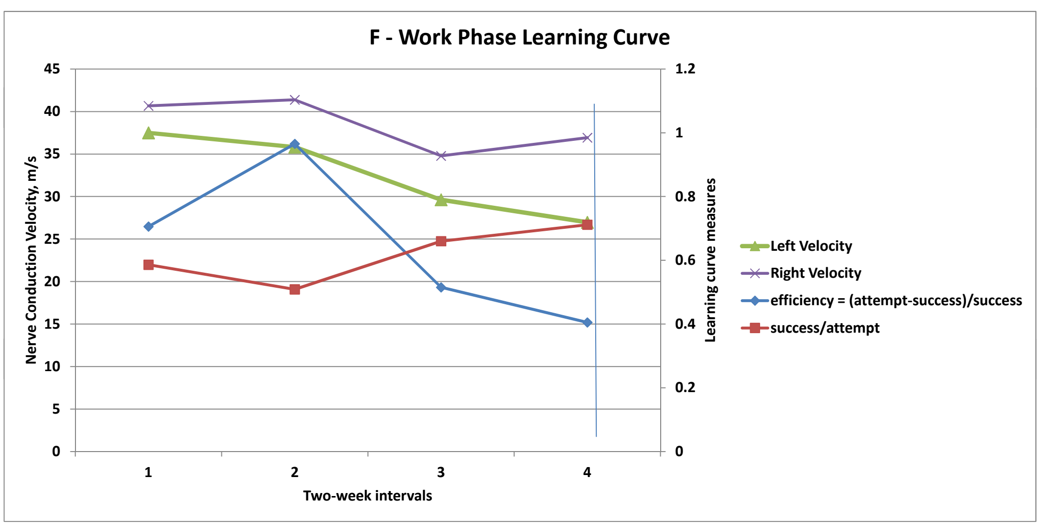
NOTES:

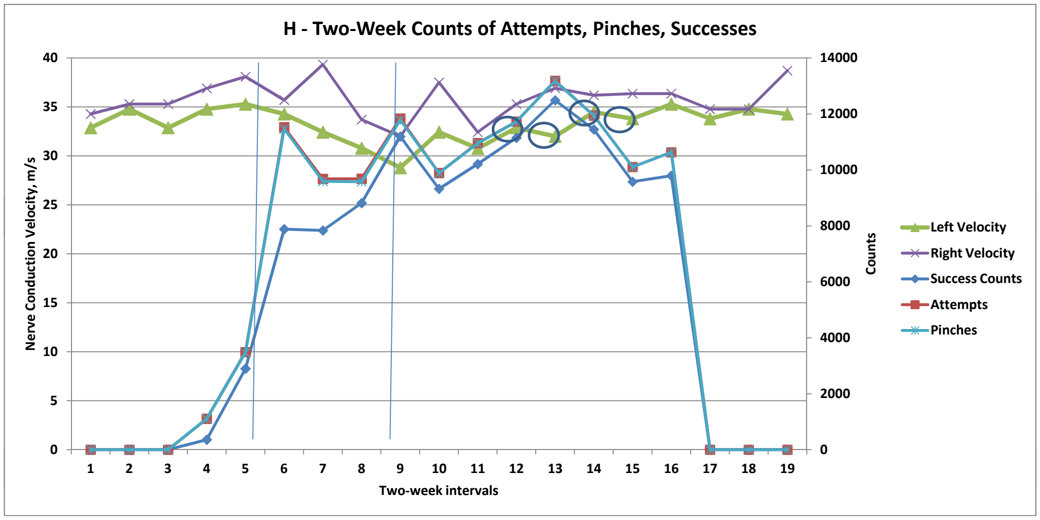
Observe steady decline in NCV with commencement of work.

Removed from task due to finger injury unrelated to work task.

NCV recovers after removal from task; speed of recovery may have been affected by administration of NSAID intermittently (circles indicate NSAID admin.).





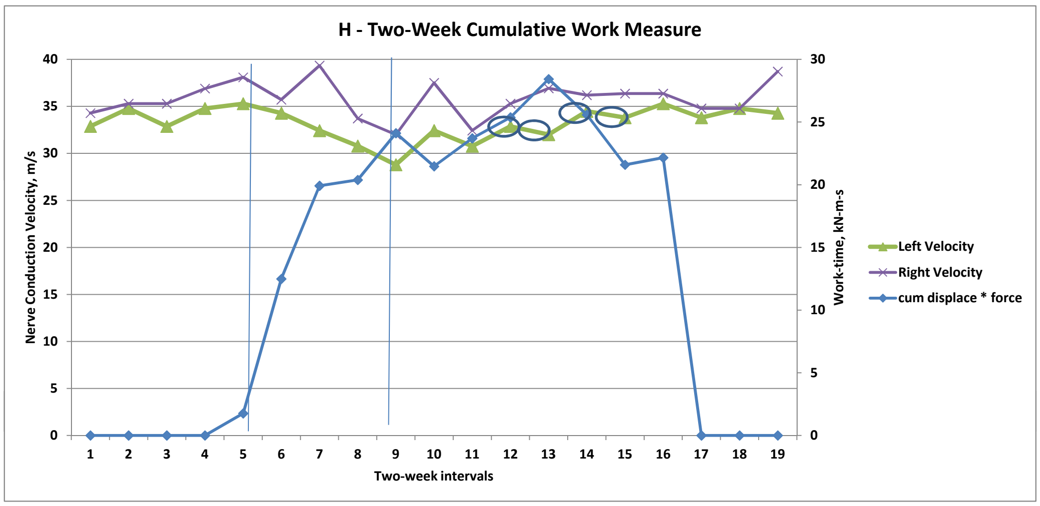


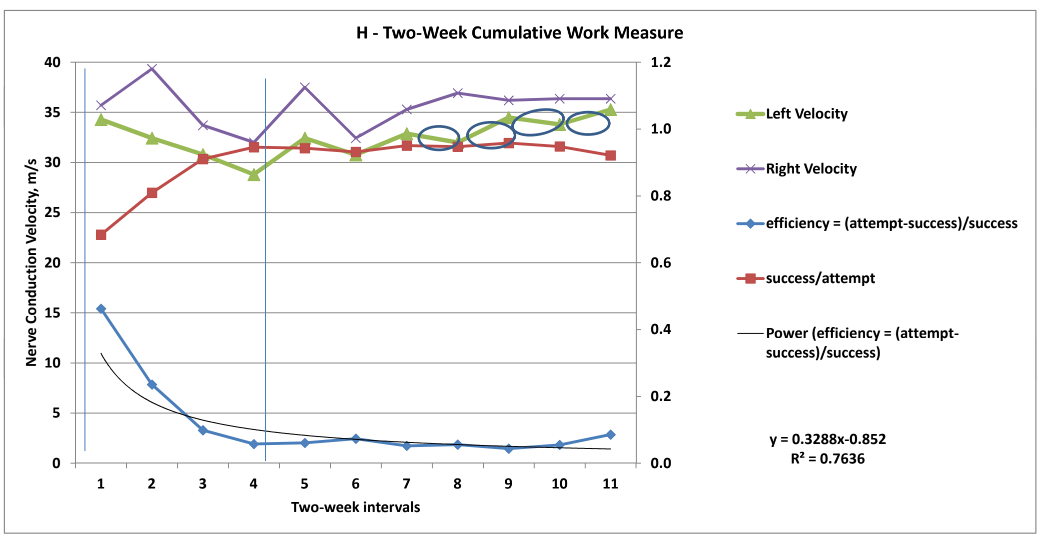
NCV declines steadily with work exposure until learning curve asymptote is reached. Beyond that point, NCV increases, though less steadily than the decline.

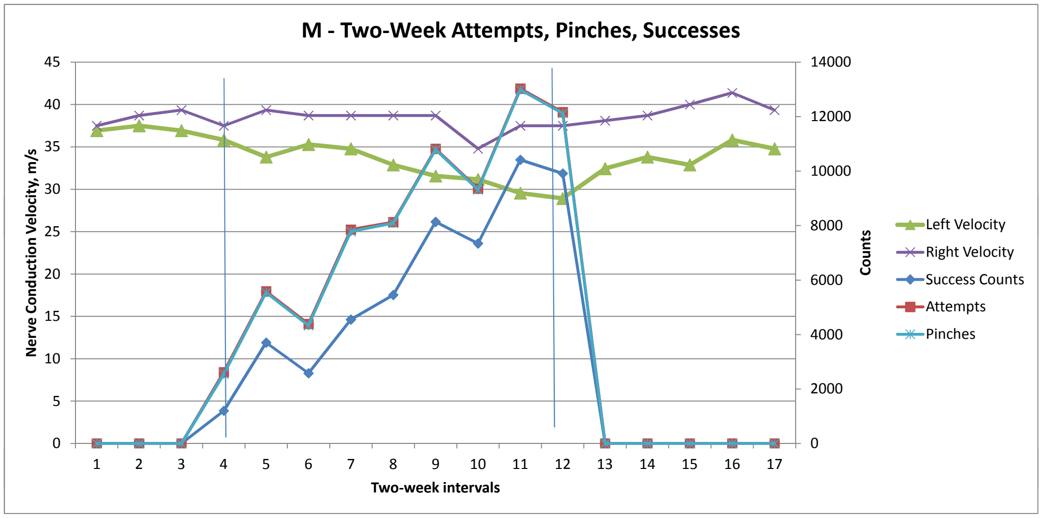
No remission is seen in the learning curve.

Efficiency is quite high at almost every data point,.

NSAIDs (circled points) were administered for reason not related to work task. NCV recovery begain prior to NSAID administration.





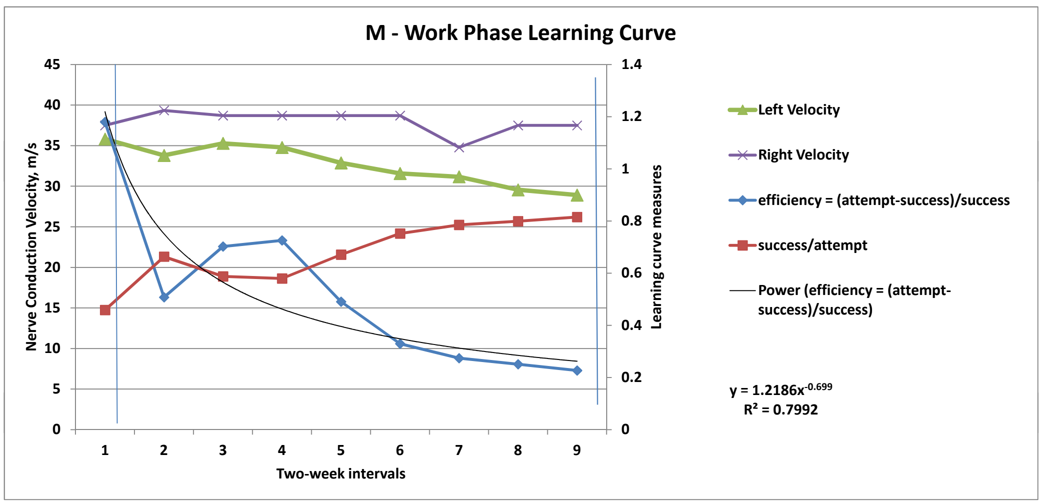


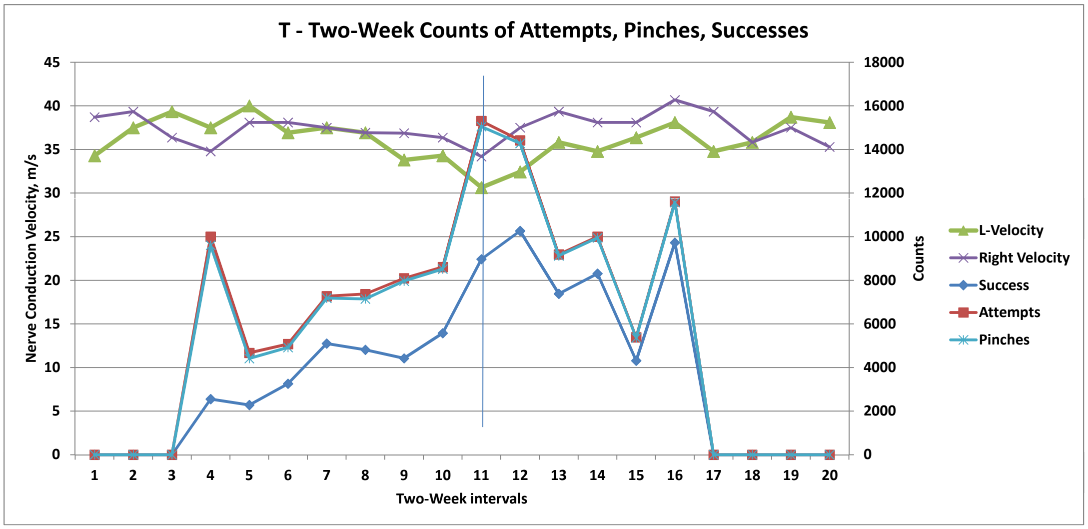
Classic NCV response to work exposure and end of exposure is demonstrated.

NCV decreases steadily over work phase.

NCV steadily increases during recovery period.

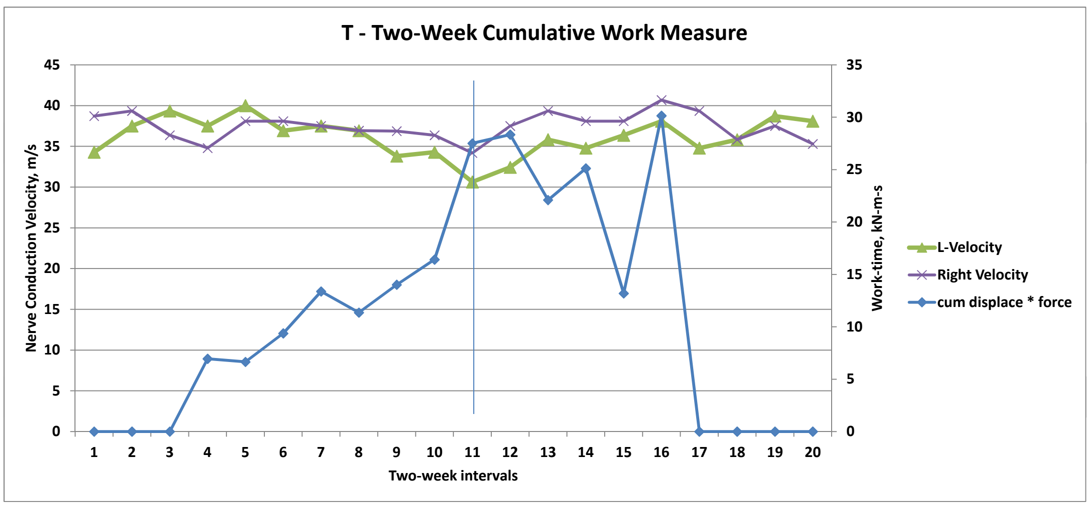
One remission is seen in the learning curve, which does not seem to achieve an asymptote during the work phase.

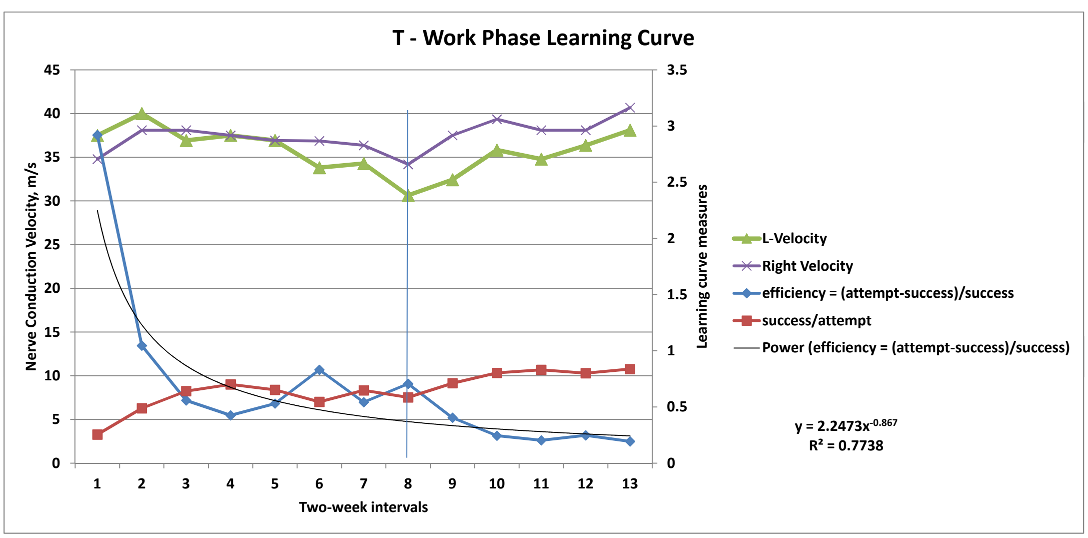


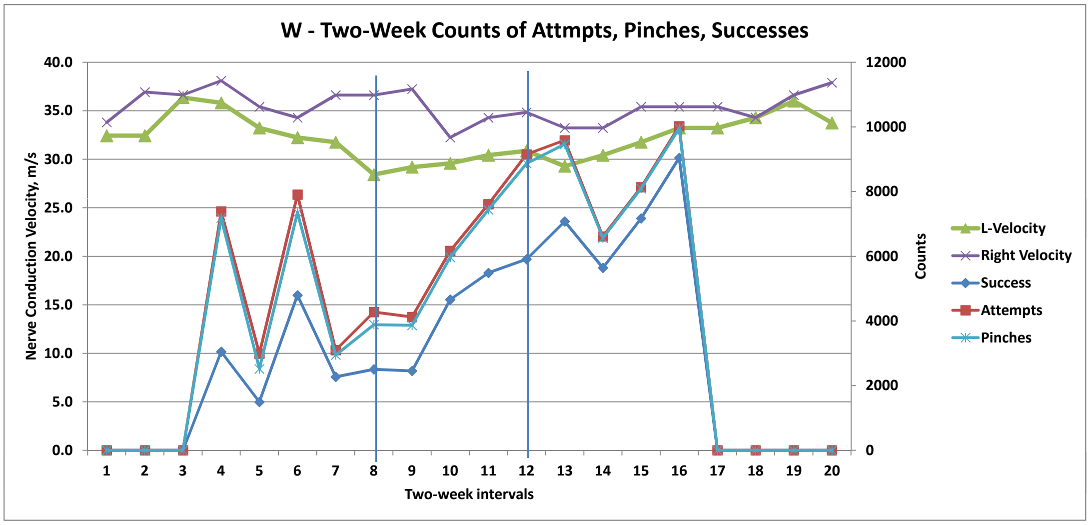


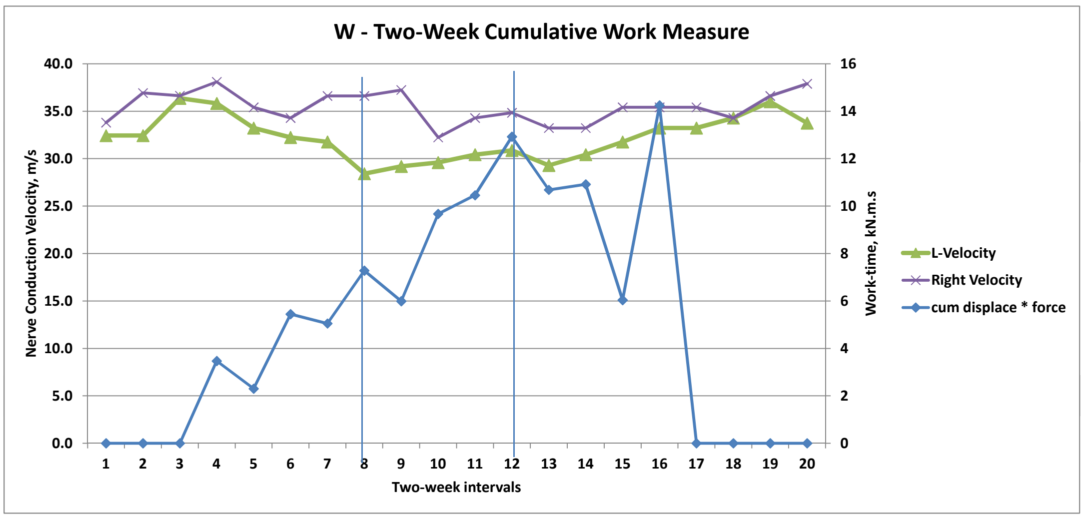
NCV begins steady decline during first half of work phase.

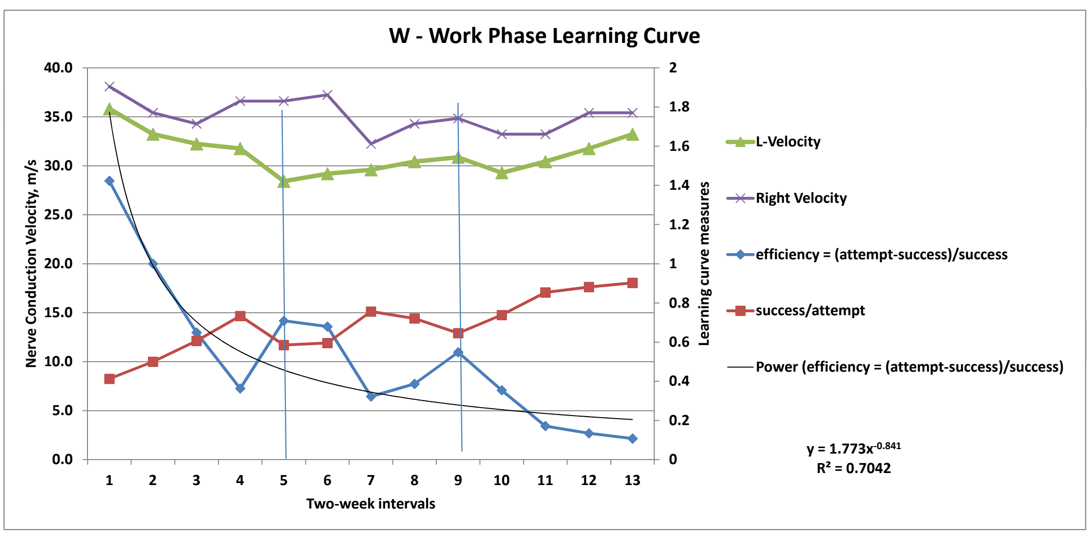
NCV begins to recover after learning curve display of remission. The almost steady increase work and repetition measures ceases, and starts an almost steady decline beyond this point, as well.









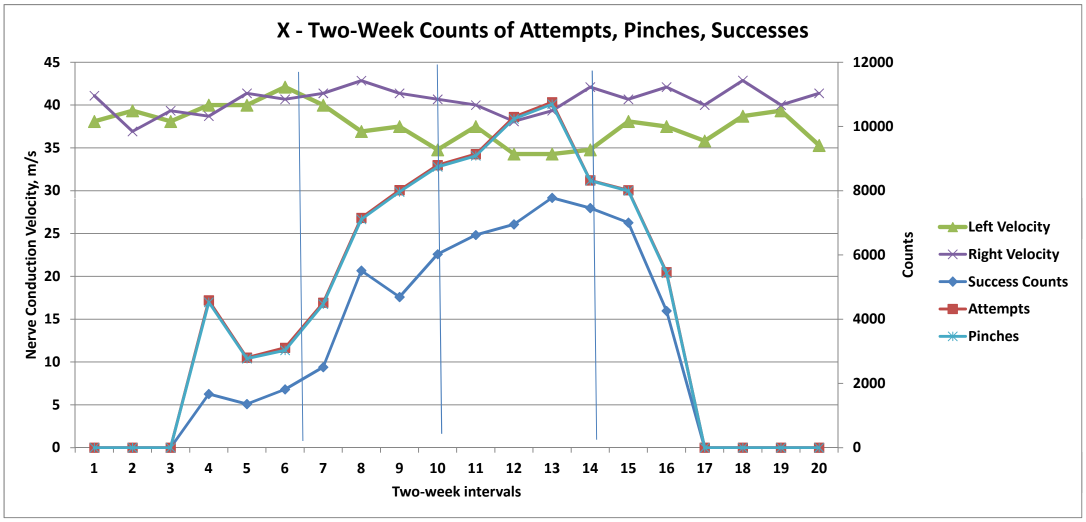


NOTES:

Steady decline in NCV with commence-ment of work.

NCV begins to recover with remission in learning curve.

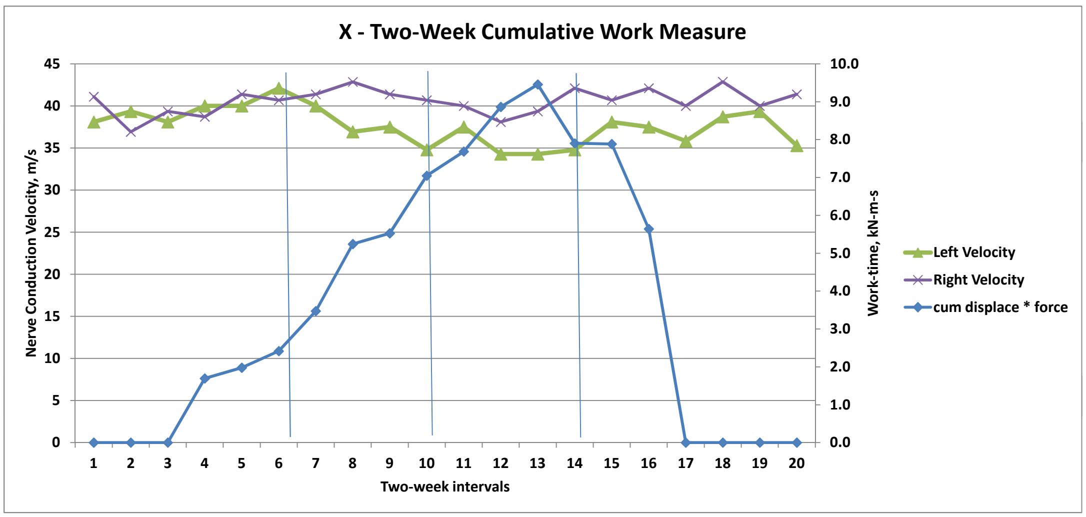
Two factor regression models with one 'count-related factor and one force-related factor, such as success count and peak pinch force, respectively, yield adjusted R2 values of 0.7 to 0.82.

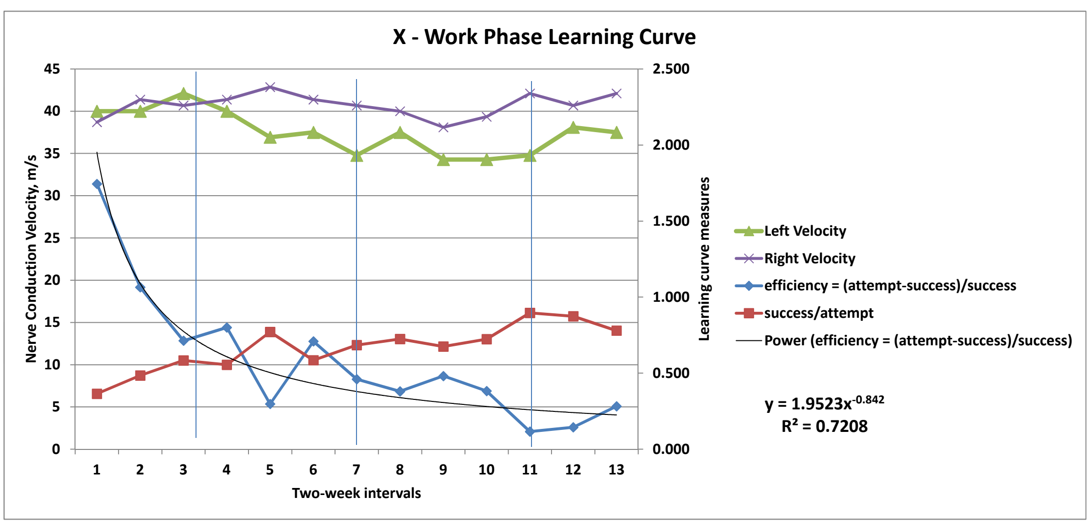


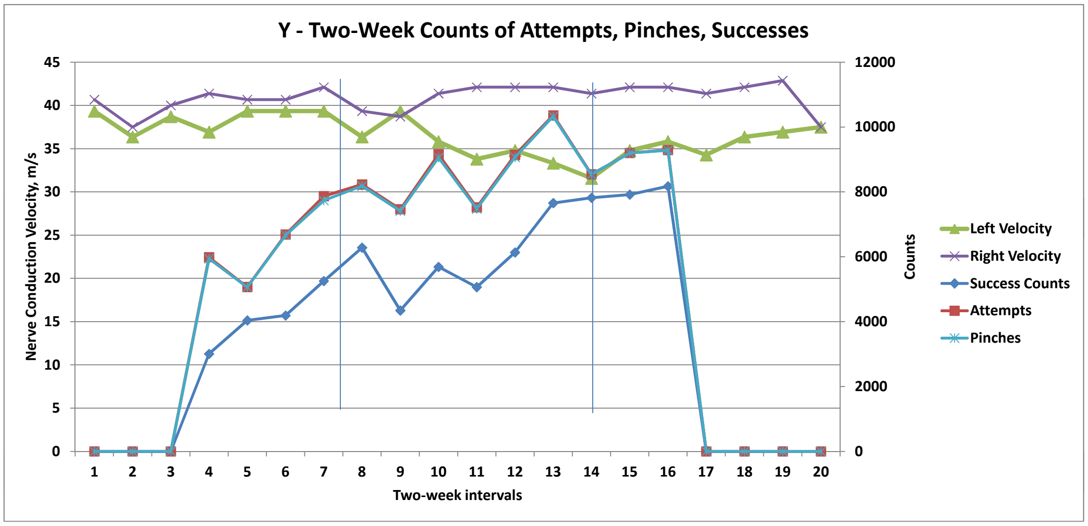
NCV declines steadily upon initiation of continued exposure to target force (first vertical ine).

NCV levels out at a reduced level after learning curve remission, and work exposure levels off and then declines.

NCV begins to recover slightly after work decline, then further still after work phase is completed.



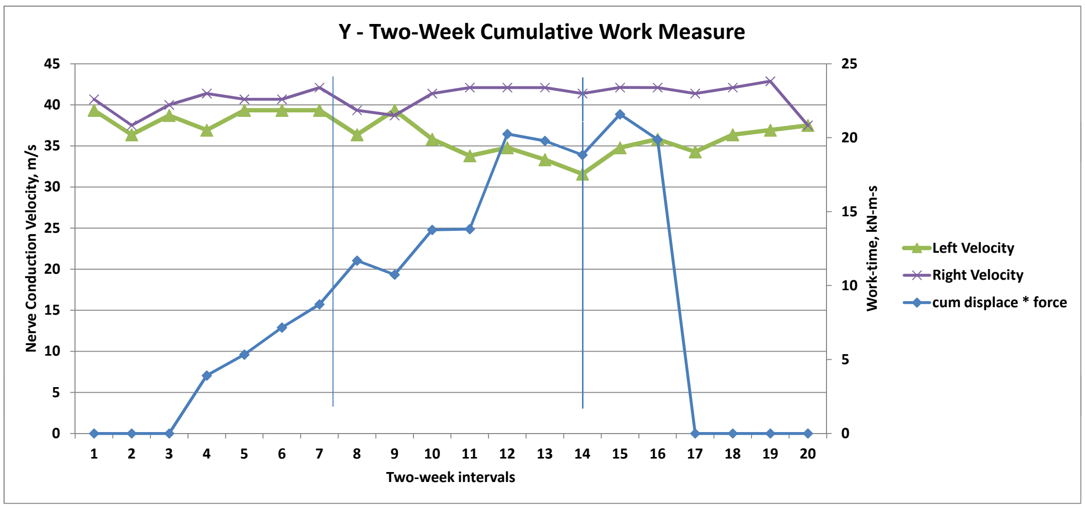


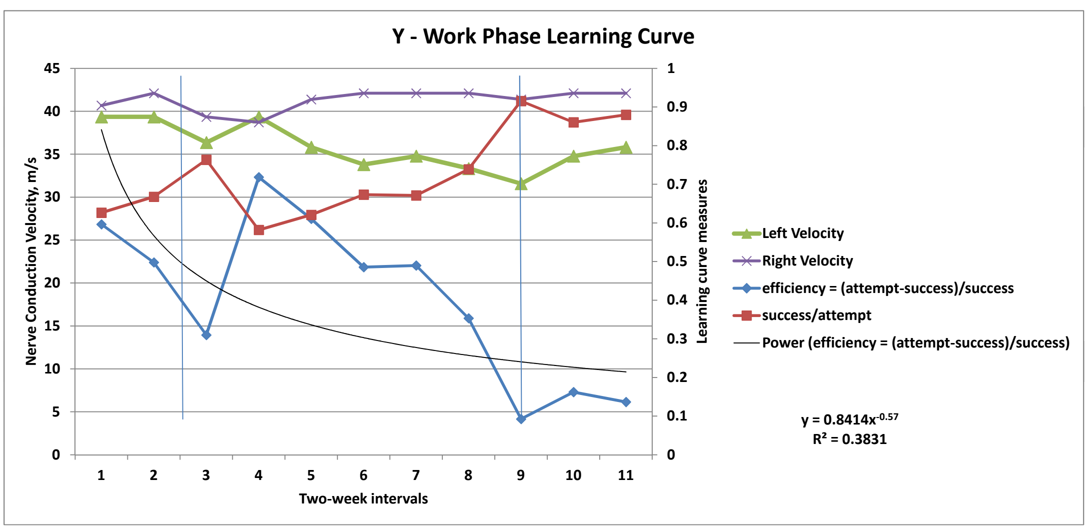


NCV begins to decrease steadily after targetted spring force is achieved (marked by first vertical line).

With exception of initial data point beyond start of target force, learning curve declines steadily, along with NCV. After learning curve reaches asymptote, NCV appears to begin to recover.

NCV recovery continues steadily following end of work phase.

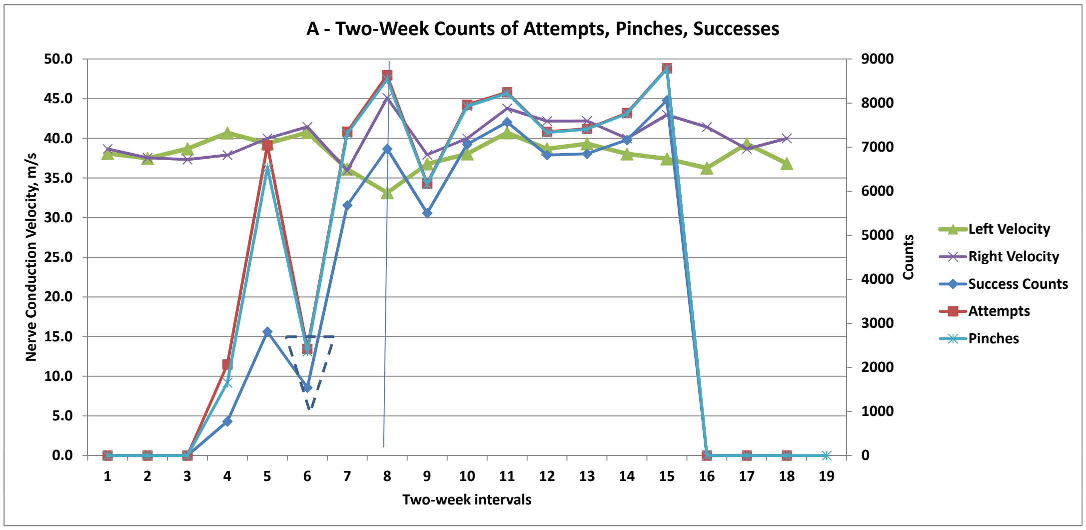


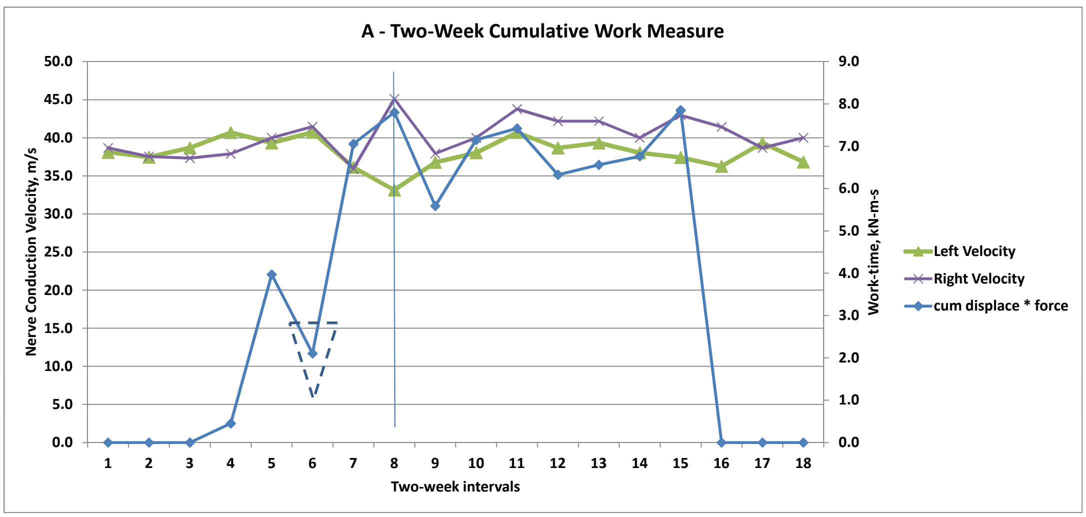


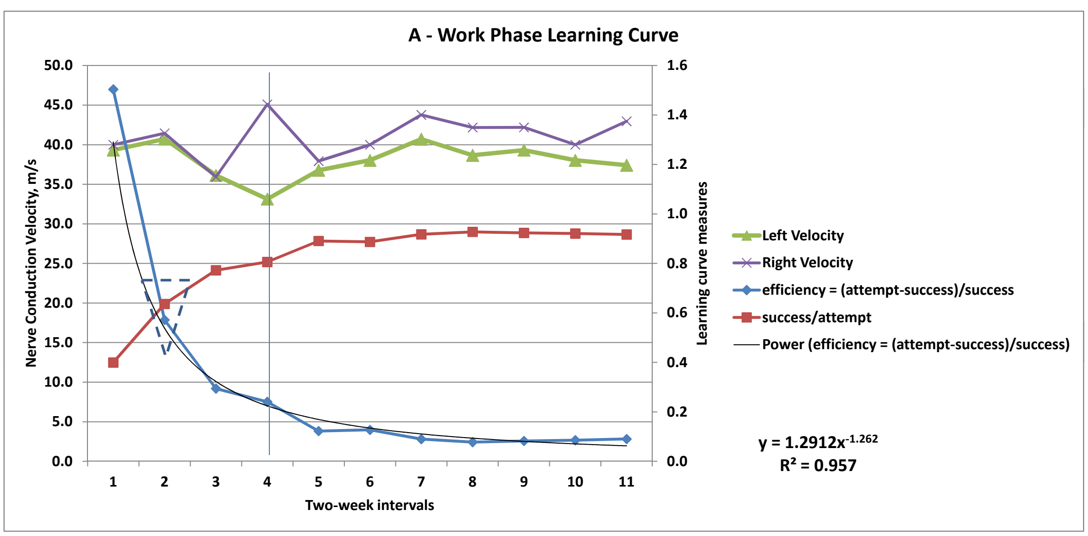
Following this page, in the PDF version of this report, there is an insertion of 4 unnumbered pages that contains examples of exposure-response graphs for some of the subjects that demonstrated a briefer decline in NCV while performing the pinch task.

In order, they are A, B, L, R.

Vertical lines are provided in the graphs, on a given page, in order to help the reader match observations (data points) across graphs.





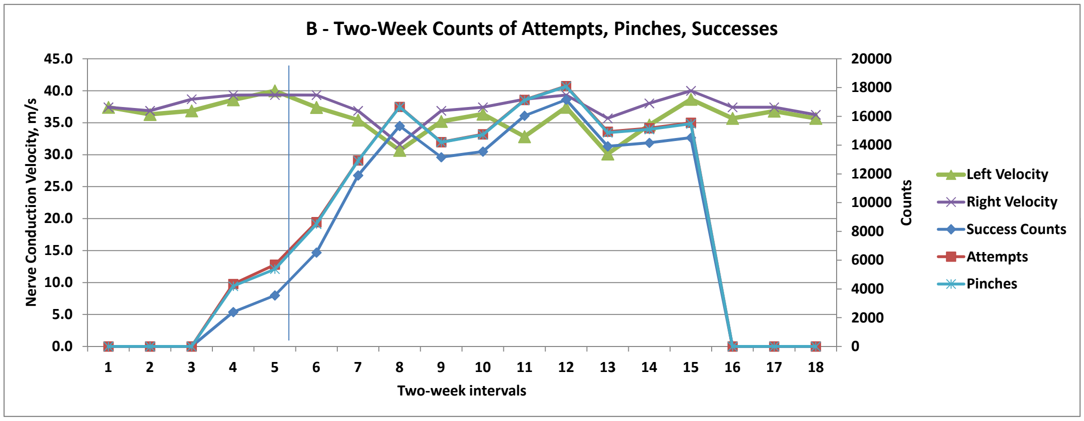


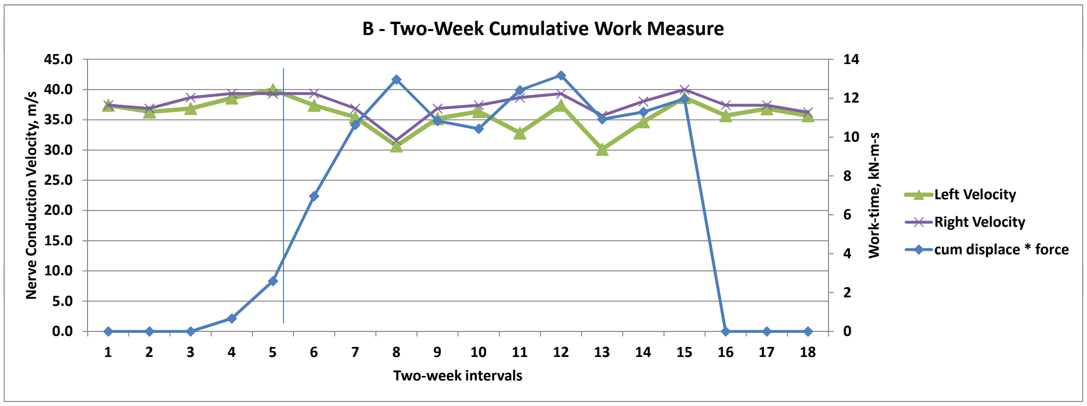
NCV declines about 17% in a 4 week period (weeks 6-8 in top and middle graphs), corresponding to commencement of task at target force.

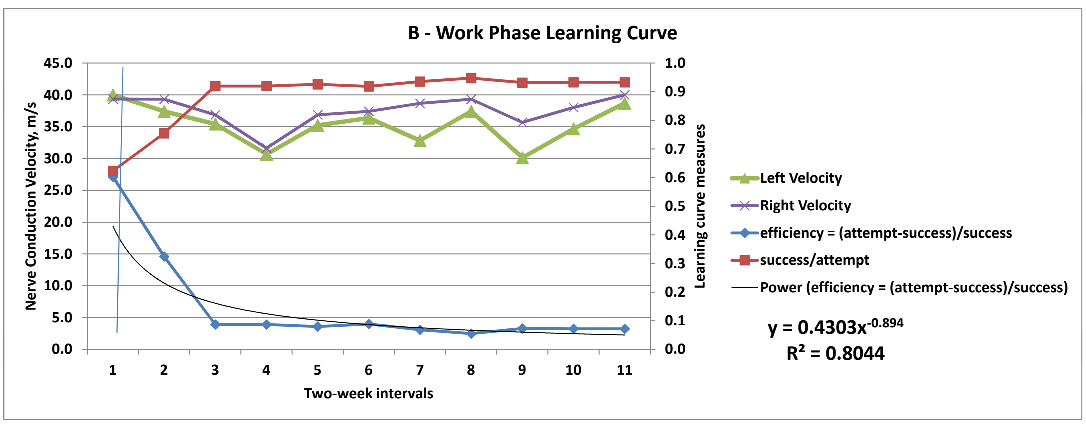
NCV appears to begin to recover about where learning curve is approaching asymptote.

No remission evident in learning curve.

Triangle marks period that includes non-work-related injury, and reduced work exposure as a consequence.





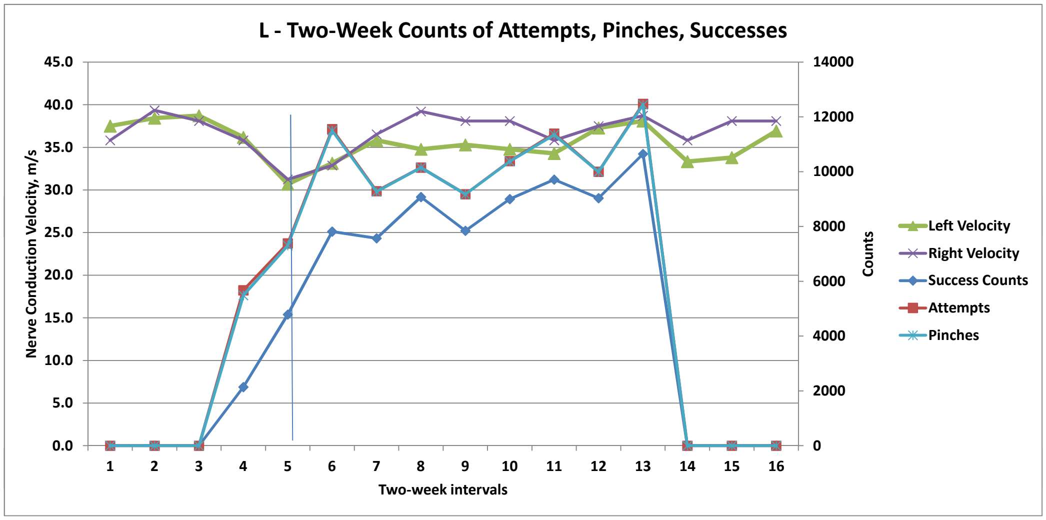


NCV declines steadily with commencement of exposure to target torque (first viertical line).

NCV begins to vascilate between increasing and decreasing during rest of work phase.

NCV recovers during work phase and remains steady during "recovery" phase.

Learning in achieved quickly and with no apparent remission.

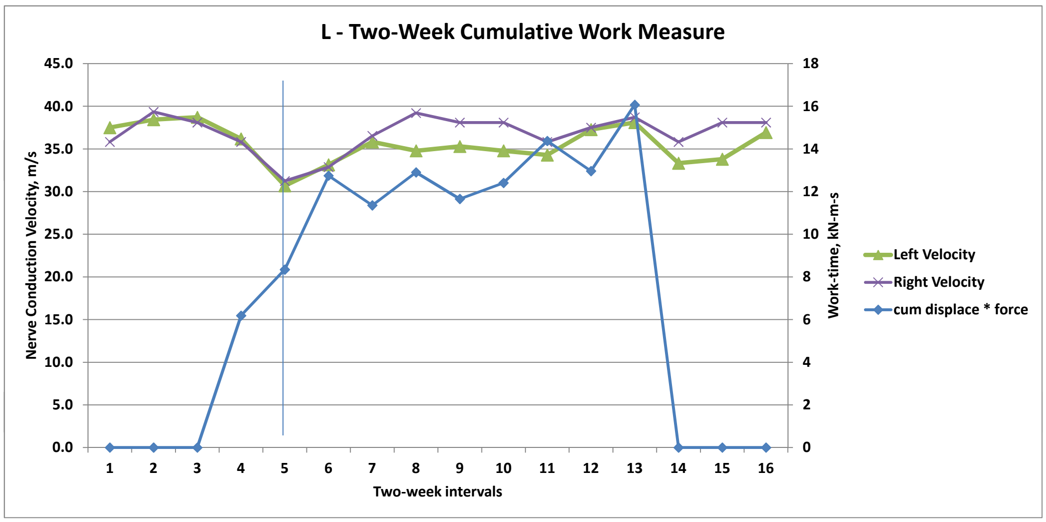


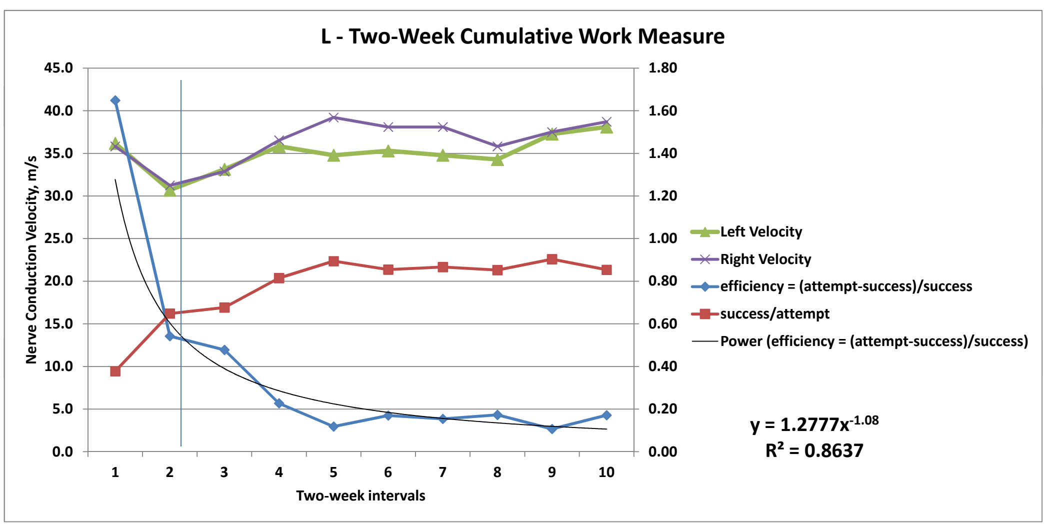
NCV appears to be affected at the commencement of the work task, but only for the first month. Beyond that time, the NCV appears to recover quickly.

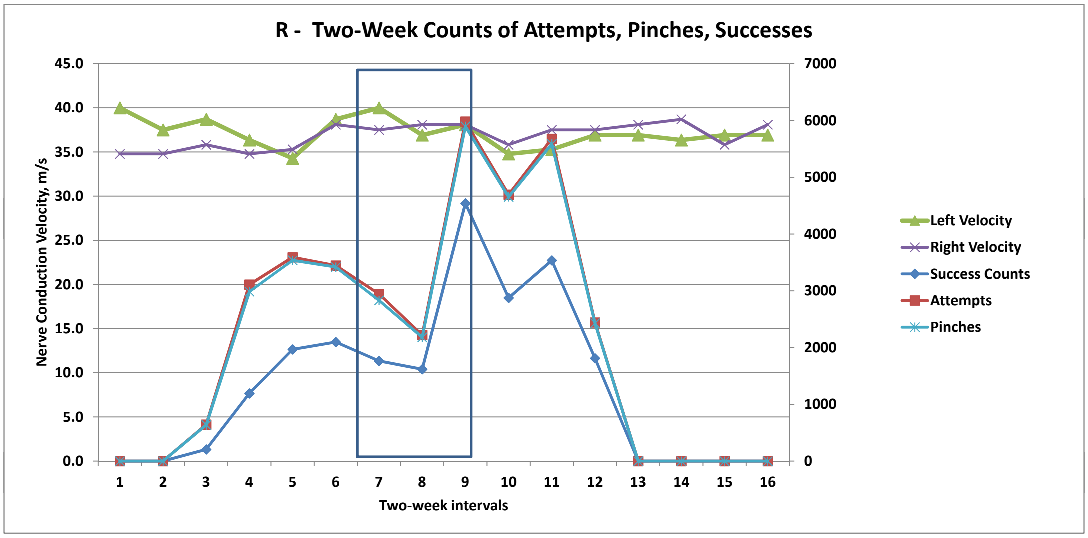
Beyond the point where NCV stops decreasing, the rate of increas in work and in the counts decreases substantially.

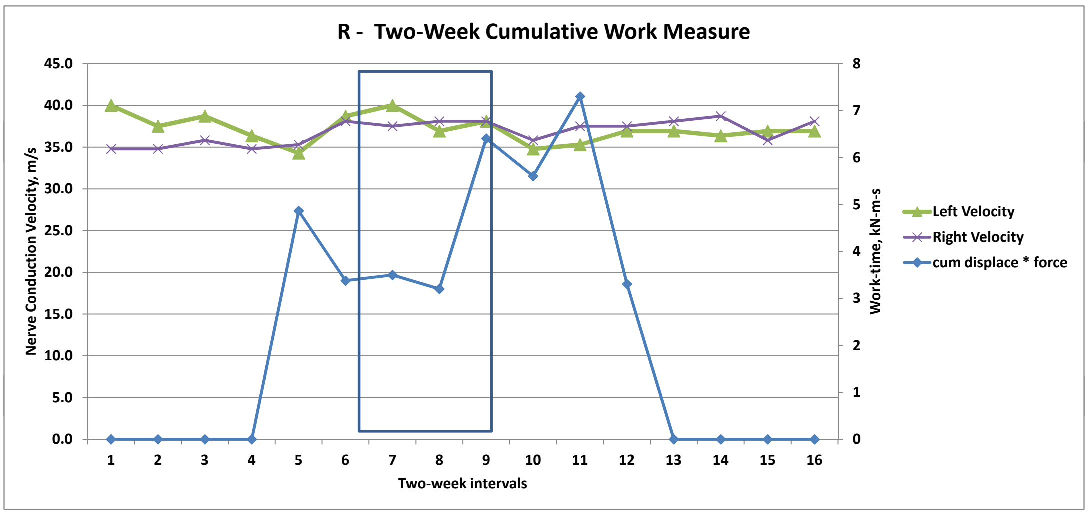
NCV recovers before the learning curve reaches its asymptote.

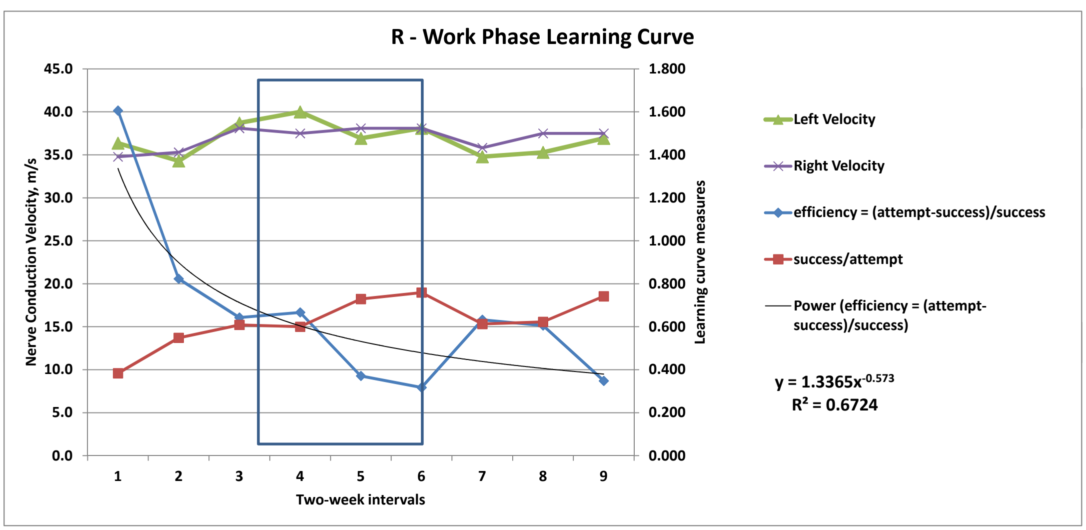
The learning curve shows no remission.











Two periods of NCV decline. Timing of first corresponds with introduction of repetition aspect of task first weeks of counts). Timing of second corresponds with introduction to target pinch force (block period).

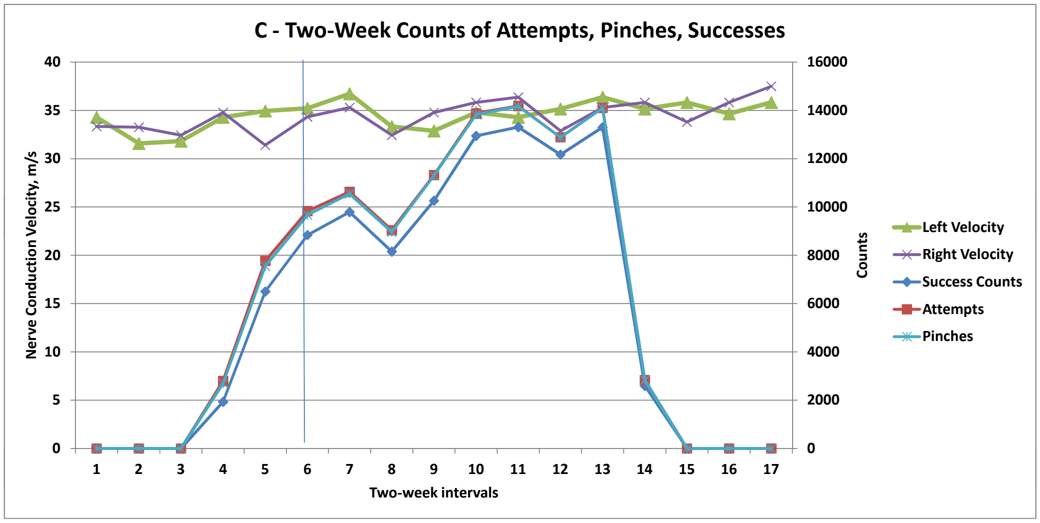
Brief and the longer remissions seen in learning curve.

Self-removed from work task (quit).

Following this page, in the PDF version of this report, there is an insertion of 3 unnumbered pages that contains examples of exposure-response graphs for some of the subjects that demonstrated no changes in NCV while performing the pinch task.

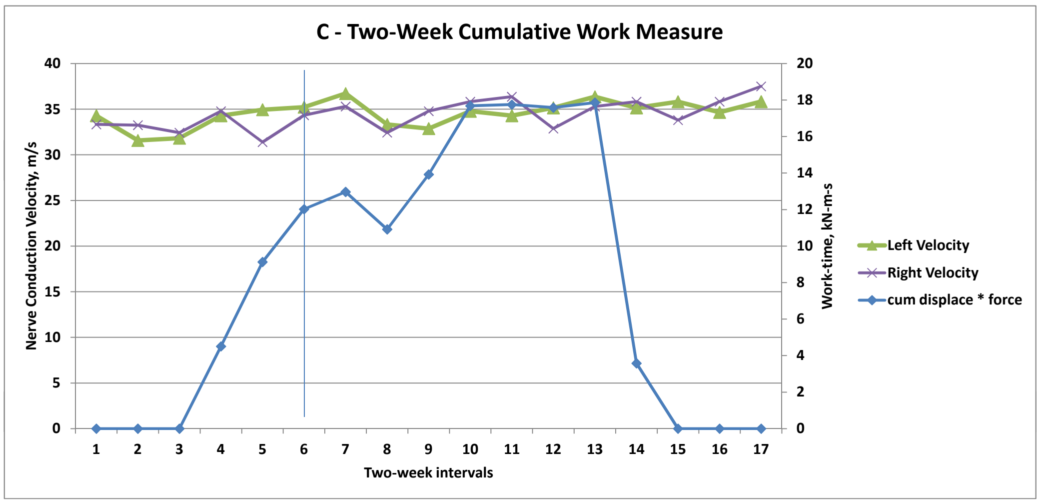
In order, they are C, O, S.

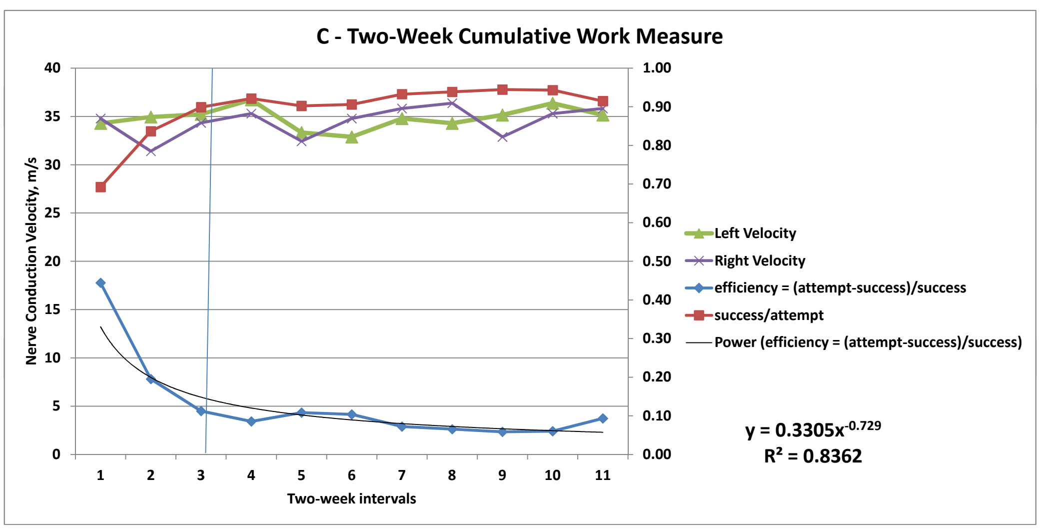
Vertical lines are provided in the graphs, on a given page, in order to help the reader match observations (data points) across graphs.

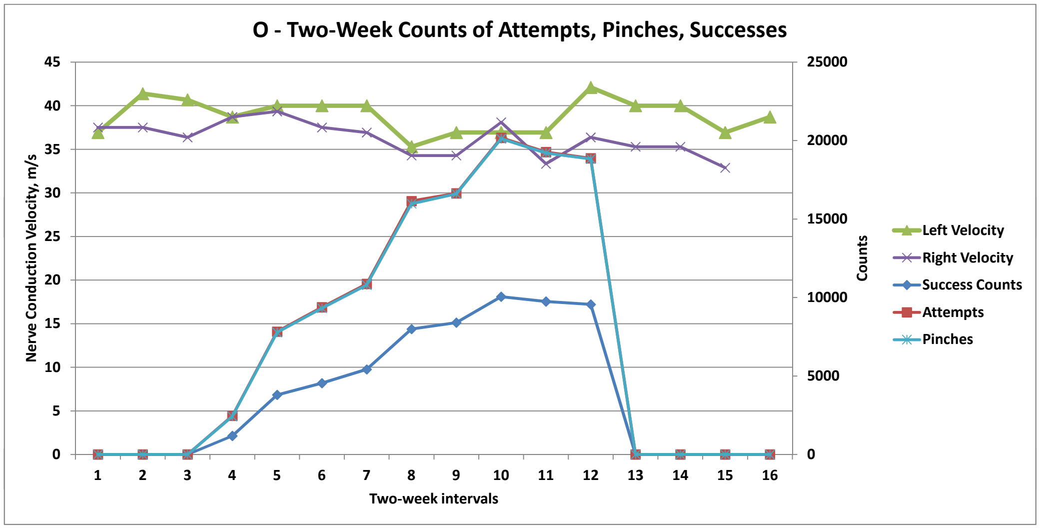


No pattern in NCV.

Learning shows high level of performance from the start. Learning curve asymptote is achieved (vertical line) quickly and with no visible remission.

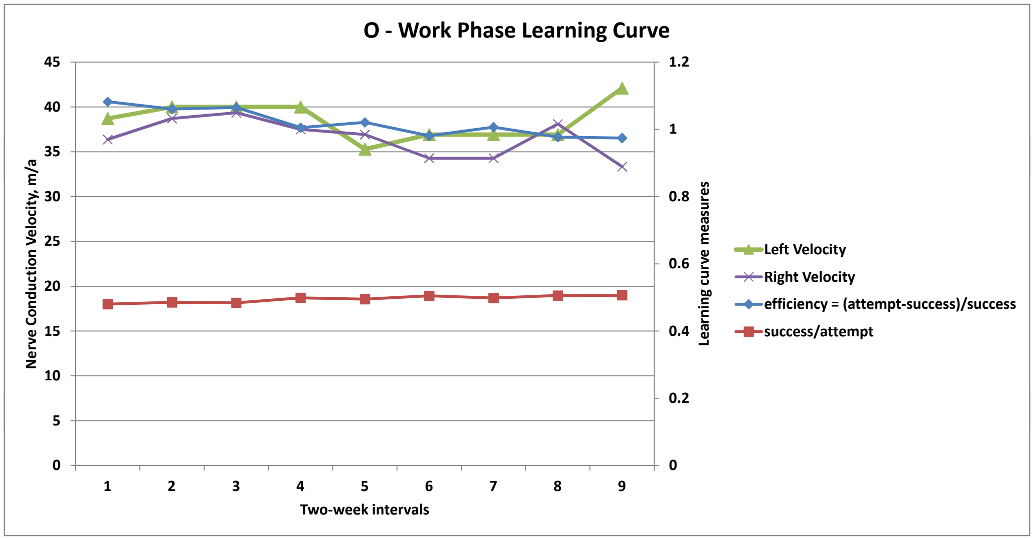


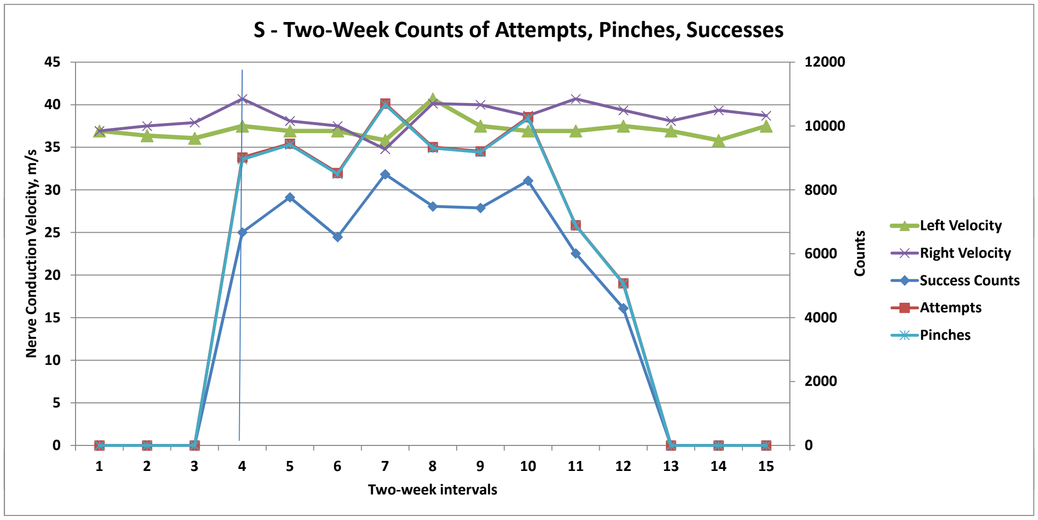




NCV does not diplay a declining trend with work exposure.

Learning (reduction in difference between attempts and successes) is not diplayed. Further, the proportion of successes to attempts is poor (about 50%).

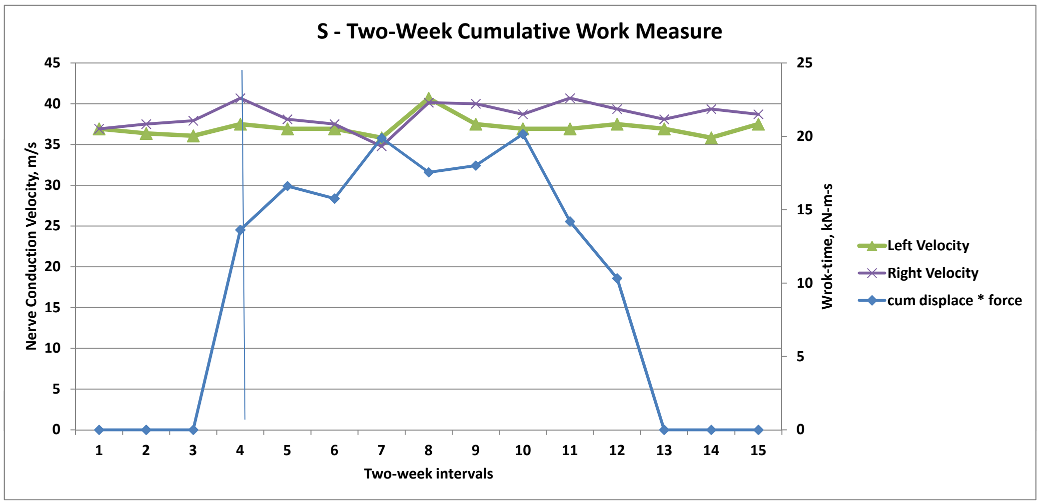


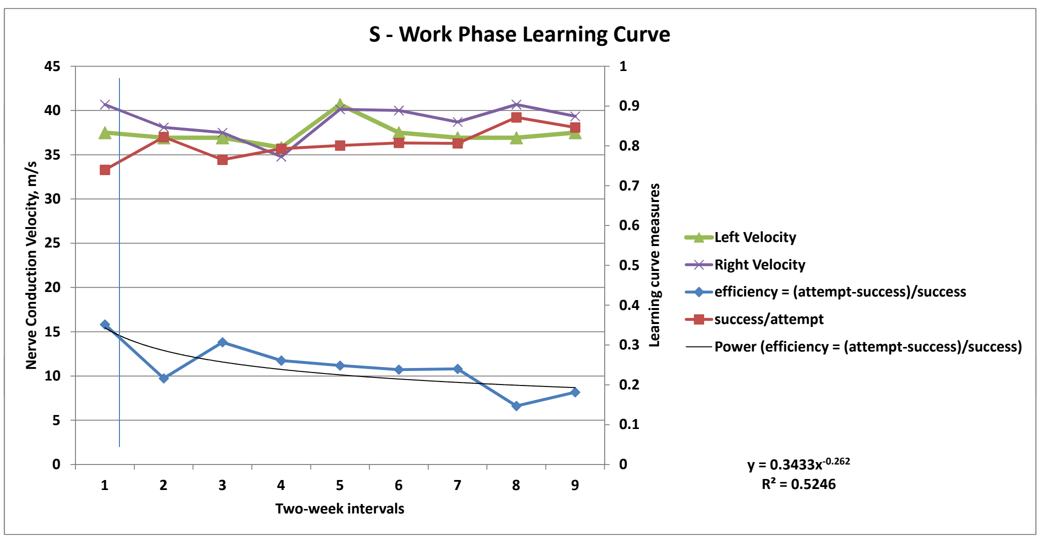


NCV remains pretty steady throughout the study period.

Work exposure is fairly steady, as wel, until last two work intervals.l. The last work period only contained 6 work days, so the two-week total was reduced, but average daily counts were lower in the last two intervals than all previous two week intervals.

Learning curve is very shallow; rate was 83%.





As can be seen in the learning curve graphs, it seems to generally be the case that when the animal reached an asymptote in the learning curve, and after any apparent learning remission (bumps in the learning curve) that NCV began to recover. M was one of only two animals that did not display any recovery in NCV until completing the work exposure period. The rate of recovery for M, 1.6% per week, was within the range of recovery rates demonstrated in the R21 study, which were 1.3, 1.4, and 2.3% per week following first bout of median mononeuropathy. The other animal was F, who was removed from the work task due to an unrelated injury. That animal was administered NSAIDs for a limited time, and that may have affected her recovery rate, which was about 3% per week. NSAIDs were also administered to four other cohort 1 animals for reasons unrelated to the work task, and at least one (H) showed NCV recovering prior to their administration and no obvious effect on NCV during the period of administration; recovery rate was pretty stead, and averaged 1.4% per week. In contrast, NSAIDs administration to E did coincide with initiation of NCV recovery and an inconsistent increase in work and task repetition. However, E's rate of recovery was only 1.5% per seek, which was similar to M's and the R21 results. Therefore, we cannot make any conclusions regarding the effects of NSAIDs on NCV or behavior from this study. Effects of NSAIDs were explored in the rat model recently for high force, high repetition tasks (Driban et al., 2011; Kietrys et al., 2011).

Results of correlation analyses for the eight subjects who showed sustained declines in NCV with exposure to the work task are presented in Table 4.4. With few exceptions, correlations were moderate to high for associations between NCV and pinch force variables, count (repetition) variables, and the work measure variable. It is interesting to note that average daily attempts was also found to be related, though less strongly, to NCV across subjects (Fig. 4.7).

Table 4.4 Results of correlation analyses for eight subjects who showed sustained declines in MCV.

	two-wk cum-ulative force	average daily 2-wk cum. force	2-wk pinch count	average daily attempts	2-wk cum. work-time
E	-0.82	-0.69	-0.84	**-0.77**	-0.81
F*	-0.96	-0.96	0.47	0.98	-0.69
M			-0.77	**-0.76**	
H	-0.54	-0.51	-0.44	**-0.10**	-0.51
T	-0.62	-0.54	-0.71	**-0.52**	-0.58
W	-0.68	-0.67	-0.46	**-0.33**	-0.36
X	-0.78	-0.64	-0.80	**-0.69**	-0.87
Y	-0.61	-0.67	-0.50	**-0.54**	-0.76

Notes for Table 4.4:

- Analysis for F was done with fewer data points than for the other subjects. For F, average daily attempts declined steadily over the work phase, which is the reason that the correlation is positive.
- Cumulative force refers to the area under the force-time curve determined from the strain gages mounted on the tongs. Work-time is related to cumulative force, as the former is the product of force and tong movement distance and time.

4.3.4 Limitations

The most important limitation of the study is that we were not able to control the experimental design to the extent we had originally planned. This limitation does not allow us to analyze our data using an ANOVA procedure to explicitly test for effects of force, posture, and the interaction of the two. However, we are able to see, from Table 4.2, that in these animals, the flexed posture seemed to be a more stressful posture. Another limitation in the study was that with the exception of one animal, recovery of NCV occurred during the work phase. We believe this may have occurred due a change we made in the design of the pinch apparatus that may have inadvertently made the task more complex, and thereby affording the animals the means to make adjustments to the way they performed the task in order to continue being successful at the task, while reducing the strain on the musculoskeletal system. We removed the hard stop that limited the travel of the tongs in the R21 apparatus, in order to be able to measure the pinch force applied to each tong in the current study. This required the subject to exert more fine control in performing the task, in that part of a successful pinch was to keep the tongs more or less centered while pinching. This highlights both a key strength and a key weakness of the monkey model of CTS, in contrast to the rat model. A key strength is the ability to model the use of the hand in many of the different ways that humans use their hands for work. However, the monkey may be able to vary the way in which the task is performed, in order to alleviate discomfort or simply make the task easier to perform and this may or may not be observable. Changes in rat behavior are readily observable for the task used in Barbe and Barr's model (Clark et al., 2004; Coq et al., 2009).

4.3.5 Summary

In summary, the study demonstrated that flexion seems to be a more problematic work posture in this model. The study also demonstrated associations between NCV decline and repetition across subjects, and within subjects across time. Associations within subjects across exposure time were also seen for pinch force variables and work (force x distance) variable. The learning curve analysis was not planned, *a priori*, but seems to show some relation between NCV changes and learning curve regions. In particular, NCV appeared to recover during periods where the learning curve was asymptotic. This may be a function of the task the subjects performed and requires more study.

4.4 Phase 3: Strength assessment

Aim 3. To expand our database of maximum voluntary pinch exertion force of the macaque, which we use to predict and set experimental levels of force (as % of maximum) in our protocols.

4.4.1 Background

A key factor associated with development of CTS in humans is the force required to perform the task. It is important to understand force in absolute terms and as a percentage of maximal strength capacity. In developing a non-human primate model of CTS, for scaling tasks to human equivalents, a method for assessing and predicting *Macaca* maximum pinch strength was needed.

In a previous study three female and one male *Macaca* (wt: 3.6 - 5.1 kg; 4.5 - 22.5 years) were trained to perform a left-handed pad-pad pinch (Banks et al., 2007). The apparatus assessed isometric pinch force with the wrist flexed to 60 deg. The equipment was functionally equivalent to that used in the work task the subjects performed in our R21 study (Sommerich et al., 2007), except the strength testing effort was isometric. Training continued until pinch force reached a plateau (about 60 training sessions) based on statistical assessment of the slope of a regression line through the three highest strengths registered.

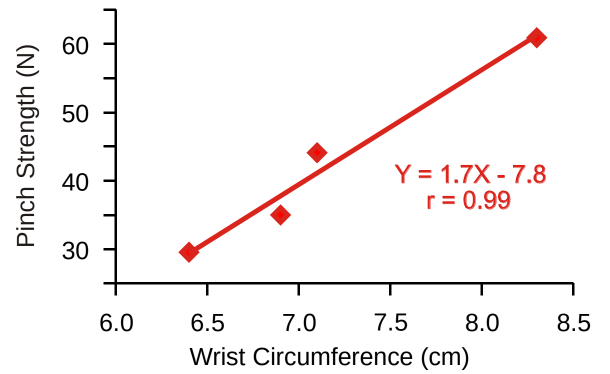


Fig. 4.8. Pinch strength as a function of wrist circumference (Banks, Lavender, Buford, & Sommerich, 2007).

Maximum pinch strength for the 4 animals ranged from 3.0 - 6.1 kg. The male displayed the greatest absolute strength. Examining several anthropometric* measures, regression analysis showed body mass and wrist circumference (fig. 4.8) were the strongest strength predictors (r=0.98 and 0.99, respectively). The results of this study were published previously (Banks et al., 2007). These regression equations have been used to scale the pinching force required for individual subjects in the R21. *(* We use "anthropometric" as a term of convenience in this document, realizing that it literally refers to human dimensions.)*

In the current study, we planned to use the relationship demonstrated above to set pinching force requirements, while in Aim 3 of the current study, we planned to develop a data base based on isotonic exertions in which the pinching movement is actually completed. We expected a similar relationship between anthropometry and force, but much faster learning to achieve a maximal effort with the new design. A redesigned strength assessment apparatus was developed for the current study.

4.4.2 Methodology

Strength data were obtained from 17 subjects as they used a custom designed apparatus that was specifically built to assess maximal pinch force in neutral, flexed, and extend wrist postures. The testing occurred after a particular subject had completed exposure and recovery so that any decrement in nerve conduction velocity return to baseline. The animals learned the task in the neutral posture and then moved on to the flexed and extended postures. The sequence of these later postural conditions depended upon their exposure during the CTS study. Although one subject failed to perform the task in the extended posture and another subject failed to provide data for the flexed posture.

A custom designed apparatus was built to allow testing of maximal pinch force. A pair of tongs like those used in the actual pinching apparatus was fitted with strain gauges and connected to bridge amplifiers that provided a voltage signal proportional to force. This signal was monitored by a computer system so that an output control signal could be produced in proportion to the pinching force. The output control signal served as the input to a device with a swing-arm that delivered food to the subject. The swing arm and the food in its delivery system were visible to the subject but could not be touched by the subject. When the harder the pinching force, the closer the swing arm came to delivering the food through a chute to the subject. Once a certain force threshold was reached, the apparatus automatically completed delivery in a predictable manner and prepared for the next trial. This apparatus was attached to the subject's cage, such that the tongs themselves were presented in an identical physical location as in the actual pinching apparatus.

Over successive days and weeks of training, the ratio between pinching force required and the movement of the swing arm was varied so that the subject would need to pinch harder as testing progressed across sessions, so that an estimate could be made of the maximal pinch force. Testing occurred 3 - 4 days a week and did not exceed 20 - 30 successful attempts in order to avoid a hypertrophy/exercise effect. Hence, this approach allowed estimation of the maximal voluntary pinching on the actual apparatus with the subject's hand and wrist in identical positions and postures as in the primary CTS experiment.

4.4.3 Results and Discussion

Figure 4.9 shows the strength distributions across subject for each of the postural conditions. On average the pinch strength was significantly different across the three wrist postures ($p<.001$). Post-hoc test found that the pinch strength in the neutral posture (mean = 25.9 N) was significantly greater than that in the flexed posture (22.7 N), which in turn was significantly greater than that found in the extended posture (16.7 N). The decrement in strength with shifts away from the neutral posture are consistent with the human literature, however, in humans three-chuck pinch strength is greater in extension than flexion (Dempsey and Ayoub, 1996; Hallbeck and McMullen 1993; Shih and Ou, 2006).

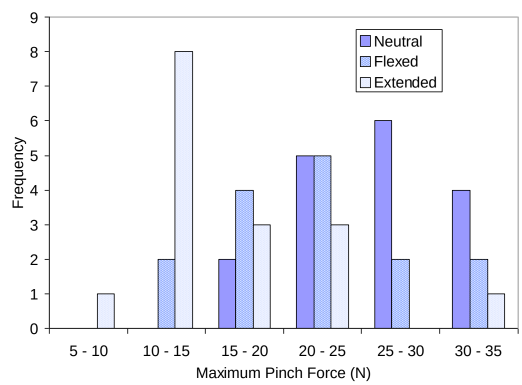


Figure 4.9 The distributions of pinch strength as a function of wrist posture.

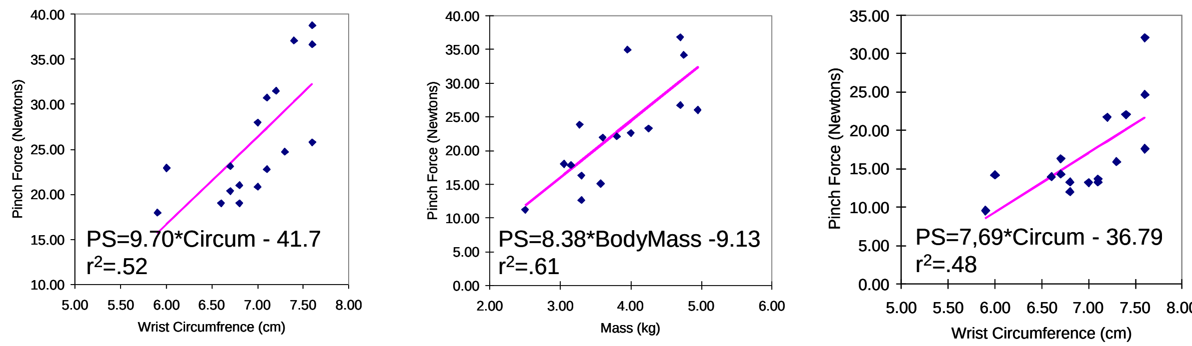
Given that the primary purpose of the strength assessment process was to determine if pinch strength could reliably be predicted based on anthropometric measures, the inter-relationships between these measures were explored. Table 4.5 shows the correlations

Table 4.5. The correlations between maximum pinch strength and the anthropometric measures of body mass and wrist circumference for each wrist posture.

	Wrist Posture		
Anthropometric Dimension	Flexed	Neutral	Extended
Body Mass	0.78	0.36	0.48
Wrist Circumference	0.66	0.72	0.69

between the anthropometric factors and strengths in the three postures. Correlations were strongest between wrist circumference and peak pinch strength for the data collected in the neutral and extended postures. In the flexed posture, body mass showed a stronger correlation with pinch strength than did wrist circumference.

Figure 4.10 shows the scatter plots of the strongest relationships and the linear regression function. As would be predicted based upon the correlations, the strongest predictive relationship was found for the pinch strength in the flexed posture. Even though the sample size was relatively small we did explore the potential of a using multiple regression model to improve the pinch strength predictions. Only the prediction of maximum pinch strength in the flexed posture improved by using both the body mass and the wrist circumference. The resulting model, shown in Equation 1, had an r-squared value of 0.69.



(a) Neutral (b) Flexed (c) Extended

Figure 4.10 The best fit univariate relationships predicting maximum pinch strength using the anthropometric dimensions of body mass and wrist circumference.

$$\text{Pinch Strength} = 6.42*\text{BodyMass} + 5.23*\text{Circum} - 38.23 \qquad \textbf{Eq. 1}$$

In comparison to the estimates from our earlier work, the results suggest a lower accessible maximal pinch strength in the context of using the device than we predicted. In that earlier study, subjects were seated in a primate chair for testing, and were able to perform isometric pinches against fixed tongs. In the present dataset, subjects were in their cage and had to move the tongs and hold them in a centered position during the pinch, just as in the repetitive work task. These additional behavioral task constraints may explain the lower apparent maximal pinch strength.

4.4.4 Limitations

The number of test sessions was limited so that this would not be a study of strength training, but rather a study of strength assessment. While this can be communicated clearly to humans, the nature of the task needs to be learned through operant conditioning techniques in these animal studies. The adequacy of the learning can be gleaned from the strength trajectory over time. It should be noted that for the most part these increased far faster than any strength gains occur, thereby indicating that we were assessing strength rather than observing a strength conditioning process. In this protocol, we assume that there is transfer between the different postural conditions with regards to the task performed by the animals which allowed us limit the number of strength assessment sessions so there would no be a strength conditioning process. While this transfer of training was generally true, there were instances where specific subjects would not work in a non-neutral posture that they had not encountered previously, which slightly reduced the sample sizes for these postures.

4.4.5 Summary

The data collected from this phase of the study is useful for expressing the relative load experienced by subjects working in the present cohort, and may also guide future studies in macaques were estimates of pinch strength would be of value. The approach of having the animal exert force in order to move a food reward closer as an obvious, behaviorally-relevant testing approach may also prove valuable to future investigations.

5. Publications. A publication is in preparation, but none are published or in press from this grant as of yet.

6. Inclusion of gender and minority study subjects. Not applicable.

7. Inclusion of Children. Not applicable.

8. Materials available for other investigators. None.

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