FINAL PROGRESS REPORT

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PROJECT TITLE: EFFECT OF REPETITION OR FORCE IN AGED RATS WITH WMSD
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SEMPTEMBER 30, 2008 REPORT

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LIST OF ABBREVIATIONS

CTGF – connective tissue growth factor
ED1 – macrophage marker
ELISA – enzyme linked immunosorbant assay
FHSR – forehead sticker removal test
HRLF – high repetition low force task
IL-1alpha – interleukin 1 alpha
IL-1beta – interleukin 1 beta
LRLF – low repetition low force task
NCV – nerve conduction velocity
WMSD – work related musculoskeletal disorders
PGP- protein gene product, a marker of nerve axons
NF – neurofilaments protein, a marker of nerve axons
CTX-1 - C-telopeptides of type I collagen cross-links
Trap5b -Tartrate-resistant acid phosphatase
C1,2C - type II collagenase neoepitopes
NC - normal control rat
TC - trained control rat
IFN gamma - interferon gamma
CINC2a – cytokine induced neutrophil chemoattractant
MIP - macrophage inflammatory protein
PGP - protein gene product of nerves, a nerve marker

ABSTRACT

Work-related musculoskeletal disorders (WMSD) account for one in three lost work time illnesses. The mechanisms of pathophysiology are incompletely understood. Animal models provide an opportunity to examine the effects of these tasks on tissues under controlled experimental conditions. In the past, we explored the effect of repetitive and/or forceful reaching and grasping in young adult rats. In this 3-year study, we extended our model to consider the effects of aging. Aim I: To determine the extent to which exposure to two task regimens, high repetition-low force (HRLF) and low repetition-low force (LRLF) causes tissue injury, inflammation, fibrosis and degeneration in musculoskeletal and neural tissues of the upper extremity in aged rats. Aim II: To determine the extent to which exposure to the two task regimens (HRLF. LRLF) causes declines in motor performance in aged rats. Aim III. To determine the extent to which the two tasks cause psychosocial behavior dysfunction in aged rats. The aged rats were 15 months of age at the time of task onset. We found that the HRLF task produced upper extremity musculoskeletal and nerve tissue damage, inflammation and sensorimotor declines, but that the LFLF task did not. Thus, we added young rats performing the HRLF task to the project for comparison purposes. We found that the HRLF task produced earlier tissue damage, and greater levels of local and systemic inflammation in aged than in young rats. The damage to bone and nerve was more pronounced in aged than in young rats and did not show recovery. Several proteins related to mechanisms of repair were down regulated in aged rats compared to young rats. Functionally, palmar skin hypersensitivity was observed almost immediately after onset of task performance. This hypersensitivity matched observed degradation of nerve endings in palmar skin. With continued performance or the HRLF task for 3 months, significant declines in median nerve conduction velocity was present bilaterally in aged rats. Progressive declines in grip strength and social interaction abilities were also evident almost immediately after onset of HRLF task performance in aged rats, as was increased aggression. The psychosocial behavioral declines resembled “sickness behaviors” and correlated highly with increased serum levels of pro-inflammatory cytokines and chemokines. In conclusion, we found that the tissue pathophysiology in WMSD is inflammatory in nature initially. A local and systemic inflammatory response appears to induce nerve fibrosis and significant declines in bone formation with continued task performance. These changes were amplified in aged rats compared to young rats. These findings have considerable importance to those designing effective prevention and management plans in older adults with WMSDs.

Highlights/Significant Findings

We were able to demonstrate a clear dose-response relationship between the performance of repetitive reaching and tissue pathophysiology as well as motor behavior degradation in carefully controlled experiments using aged rats in our rat model. Local tissue inflammation and damage was present by week 3 of task performance in rats performing a moderate demand task of high repetition, low force. Many tissue types showed evidence of inflammation and pathology as a result of task performance, including forearm tendon, muscle, peripheral nerve and bone. Tissue healing was impaired in the aged rats. Impaired healing was evidenced by fibrotic tissue healing, reduced bone formation (and therefore reduced repair), decreased innervation of palmar skin, and decreased median nerve conduction velocity. These pathological tissues changes were accompanied by declines in grip strength and palmar hypersensitivity. These latter 3 symptoms (decreased median nerve conduction velocity, decreased grip strength and palmar hypersensitivity) are each symptoms of carpal tunnel syndrome, thus further supporting a hypothesis that performance level repetitive reaching tasks induces this syndrome.

Translation of Findings

Our findings of dose-dependent pathophysiological tissue changes with the performance of repetitive motion in this rat model are consistent with the epidemiological literature implicating hand-intensive work activities in a variety of work-related musculoskeletal disorders (WMSDs). We have identified the time course for the early onset of such disorders, and have shown that local and later systemic inflammation, and then fibrosis and other types of tissue degenerative changes follow tissue injury. Each step is accompanied by declines in sensorimotor function. Elucidation of this etiology of pathology will aid the proper timing for primary preventions and secondary interventions of WMSDs. The observation that many tissue types are affected by repetitive motion suggests that appropriate interventions must consider treating more tissues than just tendon or nerve. Another key finding was the identification of the potential role for a systemic inflammatory response in propagating and prolonging localized tissue damage induced by repetitive and/or forceful tasks. As an extension of our work in the rat model, we conducted a study of serum from human subjects, and confirmed the presence of a systemic inflammatory response in workers with WMSDs and the usefulness of using inflammatory biomarkers as predictors of disorder severity. The ability to link performance variables with serum biomarkers that are indicative of underlying tissue pathology may prove crucial in identifying the stage of development of WMSDs in a patient and then in the development of appropriate prevention and treatment programs in workers, as such observations are noninvasive.

Outcomes/Relevance/Impact

Our rat model has demonstrated for the first time the early tissue changes associated with exposure to repetitive upper limb tasks that are relevant to typical workplace exposures. We have shown that early WMSD development involves a local and a systemic inflammatory component, and then tissue scarring. Such adverse tissue changes are associated with declines in sensorimotor function and abilities. These findings will aid in the design of translational studies of affected workers, and that will enable us to test various primary and secondary prevention approaches that may be translated to workplace WMSD management.

SCIENTIFIC REPORT

FINAL PROGRESS REPORT 5 R01 OH008599-03 (04/19/2007 – 09/30/2008):

Barbe, MF, Temple University

A. SPECIFIC AIMS: Aim I: To determine the extent to which exposure to two task regimens, high repetition-low force (HRLF) and low repetition-low force (LRLF) causes tissue injury, inflammation, fibrosis and degeneration in musculoskeletal and neural tissues of the upper extremity in aged rats. Aim II: To determine the extent to which exposure to the two task regimens causes declines in motor performance in aged rats. III. To determine the extent to which the two tasks cause psychosocial behavior dysfunction in aged rats.

B. STUDIES AND RESULTS.

SAI. To determine the extent to which exposure to two task regimens, high repetition-low force (HRLF) and low repetition-low force (LRLF) causes tissue injury, inflammation, fibrosis and degeneration in musculoskeletal and neural tissues of the upper extremity in aged rats.

A total of 150 aged rats (15 months old at the onset of task performance) were examined. These include experimental rats that performed the HRLF task, the LRLF task, free access to food controls that are age matched as well as age and weight matched controls (normal controls, NC), and age and weight matched controls that went through the 5 weeks of shaping but did not perform the task thereafter (trained controls, TC). We also added the examination young rats performing the HRLF task as well as normal control young rats for comparison purposes. Histochemical/biochemical analyses of bone, muscles, tendons, nerves and serum were used to determine the timing and location of tissue injury, inflammation and degeneration.

a) Systemic and local evidence of inflammation were found in the aged rats that had performed the HRLF task for 3-12 wk (n=6-12/group), but not in age-matched normal controls or in age-weight-matched trained control (rats, nor in rats performing the LRLF task (n=6/gp; data not shown). These findings included increased pro-inflammatory and anti-inflammatory mediators in serum (Figure 1, 2). The levels of serum cytokines were greater in aged rats than in young rats performing the same task (Barbe et al, 2008 and Figure 3). Increased IL-1 cytokines were also observed in local musculoskeletal tissues in aged HRLF rats (Figures 4,5); changes that were also greater than in young rats performing the same task.

b) Injury induced nerve changes in palmar epidermis and in the median nerve: In collaboration with Dr. Albrecht at Albany NY, we examined changes in innervation of palmar epidermis. We found that the training phase in which the animals learned to reach and pull the handle lever for 10 min/day for 5 weeks produced decreased skin innervation, which persisted into 3 weeks. There was recovery of trained control rats and partial recovery of aged HRLF task rats by 6 weeks (Figure 6), although nerve conduction function was not rescued in the median nerve which was significantly declined by week 12 (Figure 9).

c) Local and systemic evidence of injury and bone loss: Indicators of musculoskeletal and nerve tissue injury was present in forelimb tissues. These changes included decreased osteoactivin in muscle and tendon (Figure 5B; a protein with hypothesized anti-inflammatory properties), increased CTGF (data not shown; indicative of fibrosis) in muscle, tendon and around the median nerve. We also observed bone loss as determined by micro-computerized tomography and increased serum assays for CTX-1, Trap5b, and C1,2C (markers of bone resorption; data not shown). In contrast, serum osteocalcin, a marker of bone formation was decreased in aged HRLF rats compared to aged normal controls rats (Figure 7). Enhanced joint damage was seen in the radiocarpal joints with the onset of osteophytes in this joint as well (data not shown). There were fewer degenerative changes observed in the shoulder supraspinatous tendon than expected, even through a significant macrophage infiltration into that tendon in aged HRLF task rats (data not shown).

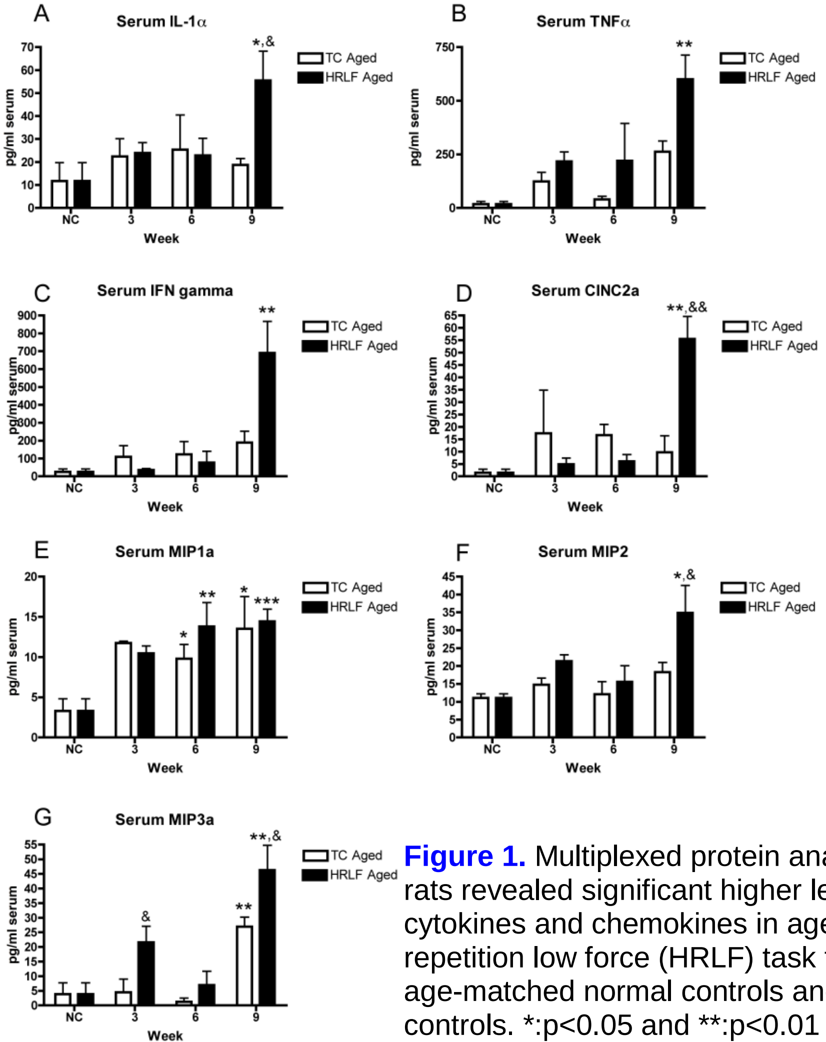


Figure 1. Multiplexed protein analysis of serum from 58 aged rats revealed significant higher levels of several pro-inflammatory cytokines and chemokines in aged rats performing a high repetition low force (HRLF) task for 3 to 9 weeks compared to age-matched normal controls and age-weight matched trained controls. *:$p<0.05$ and **:$p<0.01$ compared to age-matched normal controls (NC); $^{\&}$:$p<0.05$ and $^{\&\&}$ $p<0.01$ compared to aged matched trained controls (TC).2 way ANOVAs were performed.

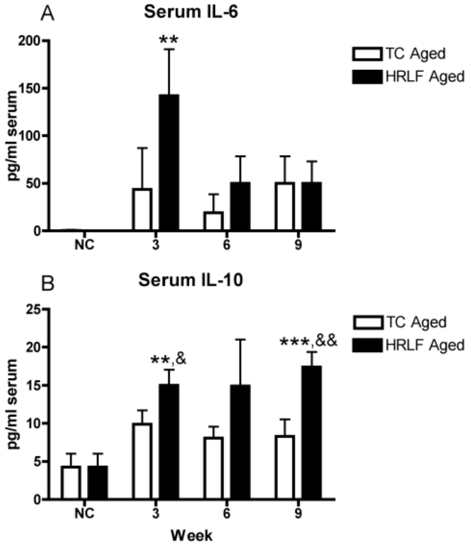


Figure 2. Multiplexed protein analysis of serum from 58 aged rats revealed significant higher levels of two anti-inflammatory cytokines in aged rats performing a high repetition low force (HRLF) task for 3 to 9 weeks. **:$p<0.01$ and ***:$p<0.001$ compared to age-matched normal controls (NC); $^{\&\&}$ $p<0.01$ and $^{\&\&\&}$ $p<0.001$ compared to aged matched trained controls (TC). 2 way ANOVAs were performed.

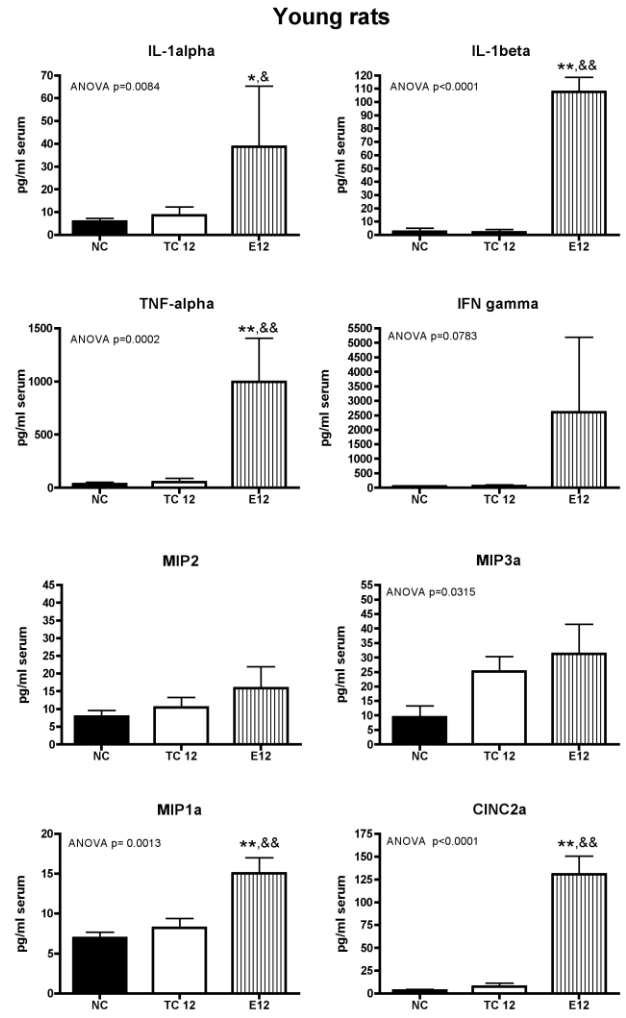
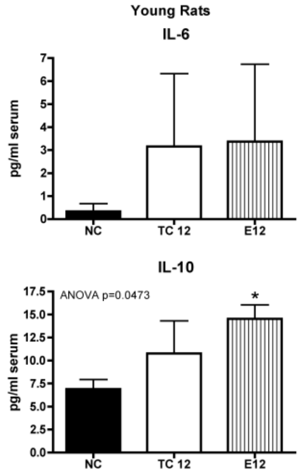


Figure 3. Multiplexed protein analysis of serum from 44 young rats revealed significant higher levels of 5 pro-inflammatory cytokines and chemokines (IL-1alpha/beta; TNF-alpha, MIP1a and CINC2a) after performing a high repetition low force (HRLF) task for 12 weeks compared to normal controls (NC). There were also higher levels of an anti-inflammatory cytokine (IL-10) in young HRLF rats compared to normal NC. *:p<0.05 and **:p<0.01 compared to age-matched normal controls (NC); $^{\&}$ p<0.05 and $^{\&\&}$ p<0.01 compared to aged matched trained controls (TC). E = HRLF task rats. Univariate ANOVAs were performed.



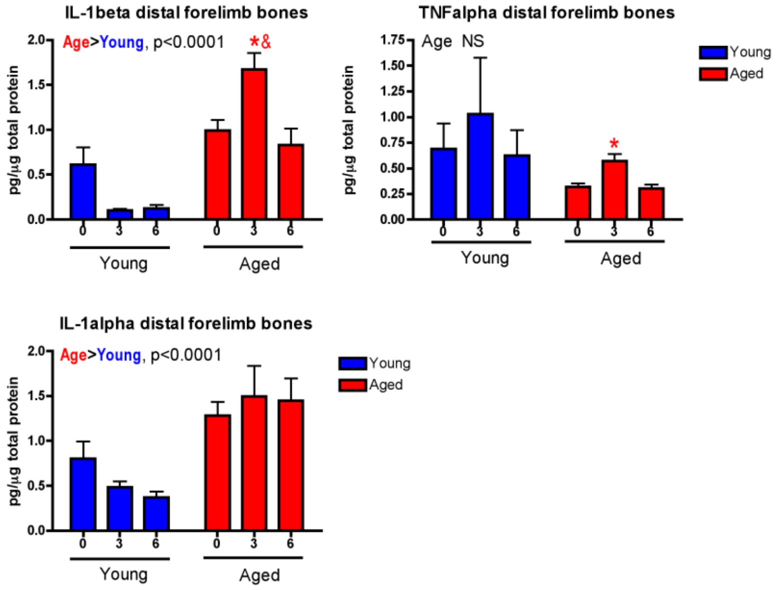


Figure 4. ELISA analysis of forelimb bones (radius and ulna) from young and aged performing a HRLF task revealed significant higher levels of 2 key pro-inflammatory cytokines, IL-1beta and IL-1alpha, in the aged HRLF rats compared to control aged rats (0) and compared to young rats. *:p<0.01 compared to aged matched normal controls, called 0 week; $^{\&}$ p<0.01 compared to young rats performing the same task for the same length of time. 2 way ANOVAs were performed. n=4-9/group.

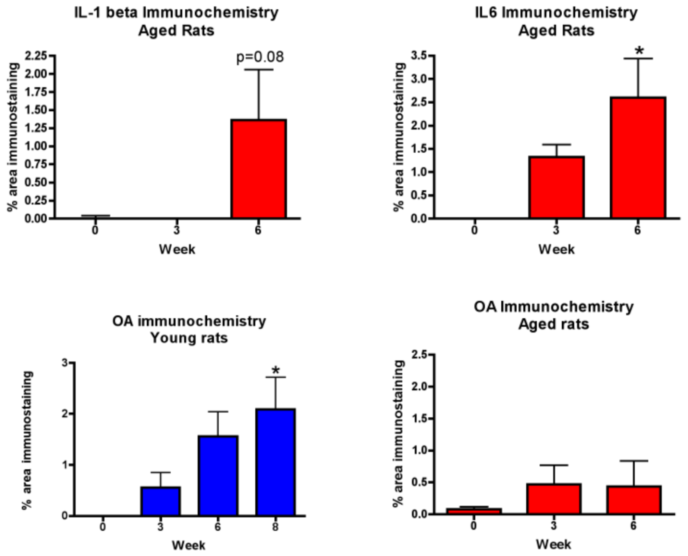
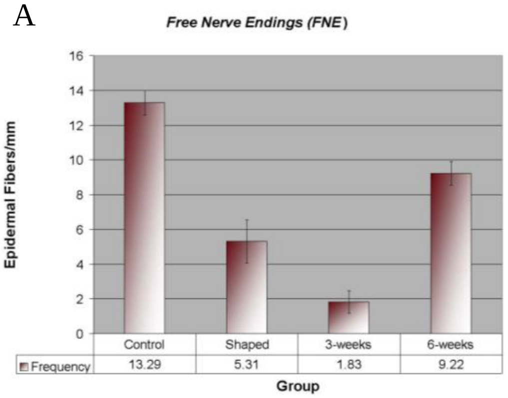


Figure 5. ELISA analysis of forelimb flexor muscle aged rats performing a HRLF task revealed significant higher levels of a key pro-inflammatory cytokine, IL-1beta, as well as IL-6, a proteic cytokine and myokine. The increase in IL-6 is suggestive of glycogen depletion in muscle of 6 week aged HRLF task rats. In contrast, osteoactivin (OA) was greater in young rats than aged rats. The meaning of the increase in OA has yet to be determined. *:p<0.01 compared to aged matched normal controls, called 0 week. Univariate ANOVAs were performed. n=4-9/group.

A



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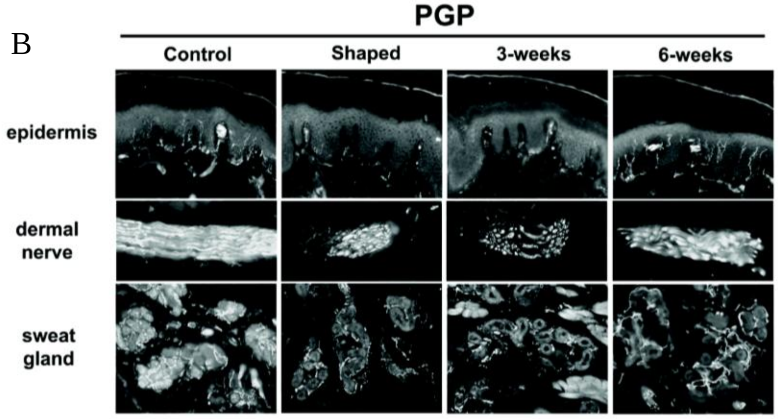
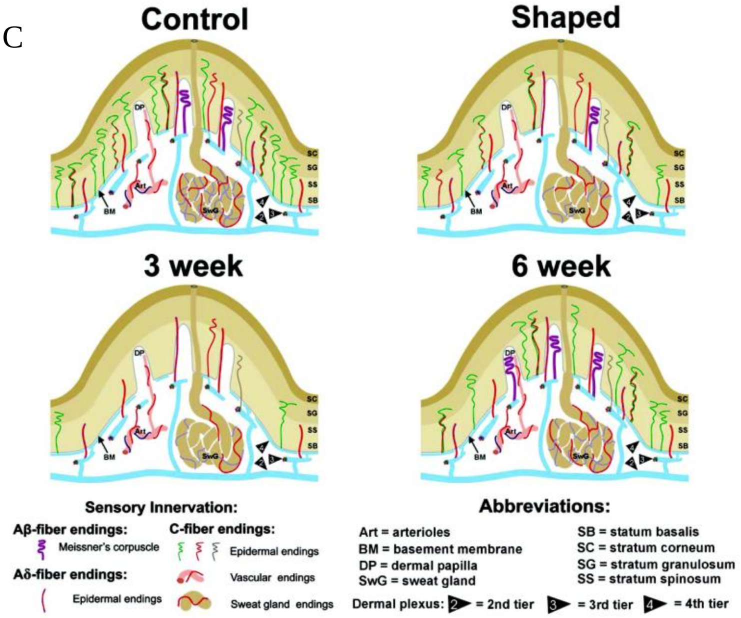


Figure 6A-C. Free nerve endings in the palmar epidermis of the aged rats decreased significantly in the shaped only rats (trained control rats) and in 3 week aged HRLF rats. Free nerve ending innervation to the epidermis recovered towards normal levels by 6 weeks, but did not recover entirely. n=4/group.

C



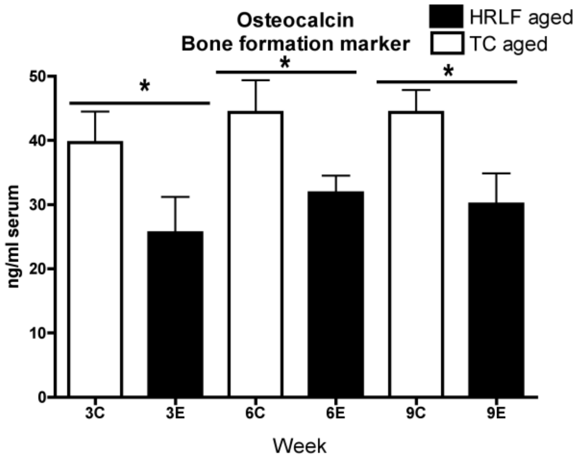


Figure 7. Osteocalcin serum levels, measured using ELISA, were significantly lower in the aged experimental (E) rats performing a HRLF task for 9 weeks compared to trained control aged rats. *:p<0.01 compared to aged matched trained controls. The decline in osteocalcin is indicative of declining bone formation. A univariate ANOVA was performed. n=6-9/group.

SA II: To determine the extent to which exposure to the two task regimens (HRLF. LRLF) causes declines in motor performance in aged rats.

Motor tests: We performed a forelimb grooming function (forehead sticker removal test), an analysis of pathological movement reversals using a movement analysis system; and grip strength. We found a decline in grip strength in the preferred reach limb immediately after task training (TC), and at 3 and 6 weeks of performance of the HRLF task in the aged rats (Figure 8). We also observed a slight improvement by 6 weeks, matching temporally the partial recovery of nerve damage shown above in Figure 6. We did not observe a significant decline in grip strength in aged normal control rats compared to young normal control rats.

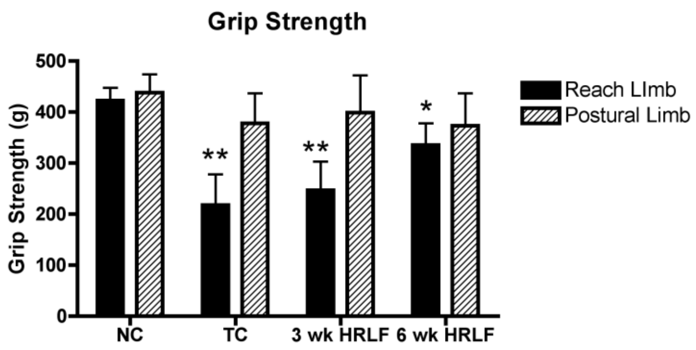
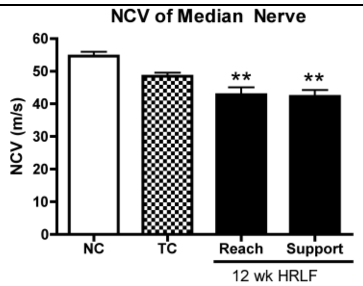


Figure 8. Effects of HRLF task on sensorimotor behavior in aged rats. Grip strength did not decrease, but the withdrawal threshold (Von Frey test) decreased significantly, indicative of mechanical hypersensitivity. *:p<0.05 and **:p<0.01 compared to aged matched normal controls (NC). TC = trained controls. A 2-way ANOVA was performed. n=9-10/group.

Injury induced nerve dysfunction: We are performed nerve conduction velocity (NCV) testing to examine the effects of performing repetitive tasks on the median nerve. We observed no significant declines in NCV in aged normal control (NC) rats compared to young NC rats (50 m/sec; p>0.05), and no significant declines in aged TC rats compared to aged NC rats. However, there were significant differences in the median nerve NCV in aged rats performing the HRLF task for 12 weeks, bilaterally (Figure 9). This decline in NCV shows that despite the recovery of some of the nerve innervation patterns (see Figure 6), that nerve dysfunction persisted.

Figure 9. Effects of HRLF task on median nerve conduction velocity (NCV) in aged rats. NCV was significantly decreased bilaterally in aged rats performing the HRLF task for 12 weeks, but not in rats that underwent the shaping only (TC) or in normal controls rats (NC). **:p<0.001 compared to NC. A univariate ANOVA was performed. n=10/group.



Sensory test: We added a sensory function test to this project (Von Frey test for palmar skin mechanical hypersensitivity or hyposensitivity). By week 6 of HRLF task performance, hypersensitivity was evident bilaterally, as evidence by a decreased withdrawal threshold (Figure 10). This hypersensitivity was still evident by week 9. Our histological assays show this is due to fibrotic tissue changes in and around the median nerve (data not shown).

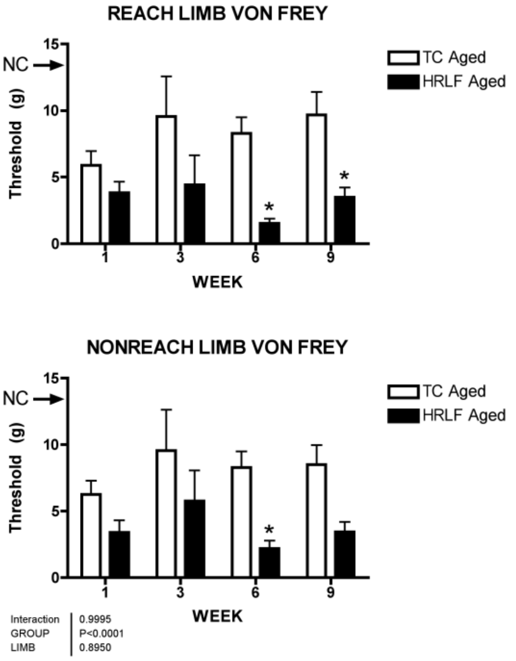


Figure 10. Von Frey threshold in grams (g) in age-matched normal controls (NC, arrows), age-weight matched trained control (TC) and HRLF rats. A univariate ANOVA was performed. *:p<0.01 compared to NC and TC. n=10/group.

SA III: To determine the extent to which the two tasks cause psychosocial behavior dysfunction in aged rats.

Social interaction abilities significantly declined in weeks 3 though 12 in the HRLF aged rats, but not in age-weight matched trained control rats (Figure 11). Similar declines in social interaction abilities were observed in young HRLF rats only by 9 weeks of task performance. Signs of increased aggression were evident in aged rats immediately after training (trained control (TC) rats) compared to age-matched normal control rats (NC, arrows); aggression was increased in HRLF rats by week 1 and remained elevated. Young rats showed much lower signed of aggressive with HRLF task performance (Figure 11). We observed no declines in psychosocial behavior in LRLF aged rats (data not shown).

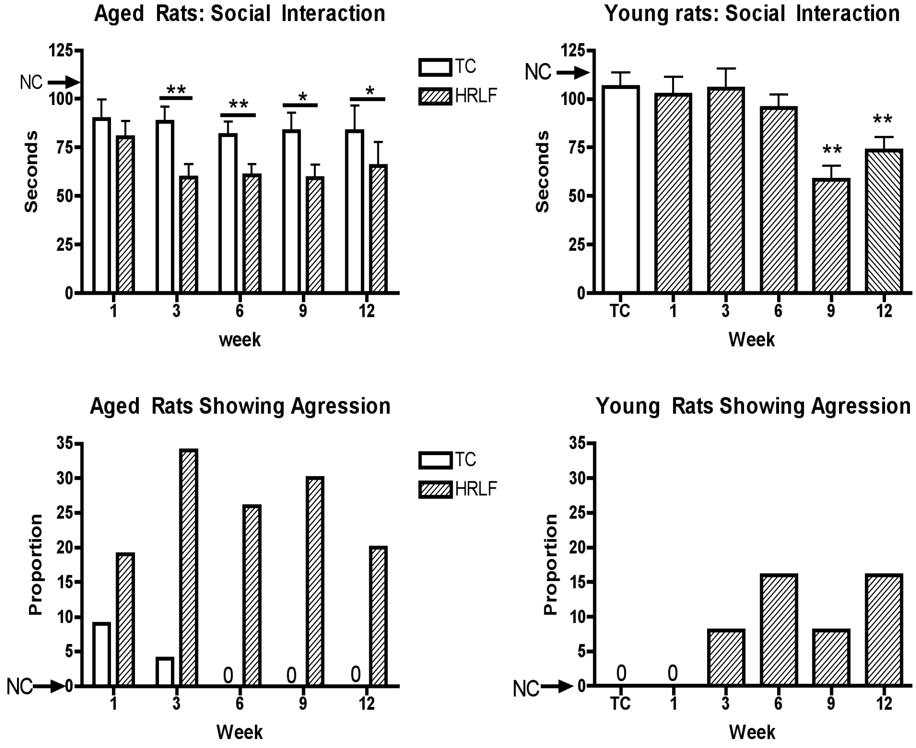


Figure 11. Social interaction test was performed by placing adult rat with novel juvenile rat and observed seconds in which the adult rat spent grooming or sniffing the juvenile rat. Signs of aggression were noted and the test was ended immediately. The proportion of adult rats displaying aggression is shown. Normal control values indicated by NC and arrows. *p<0.05 and **p<0.01 compared to age-weight matched trained control rats.

C. SIGNIFICANCE: These results show that performance of moderate demand repetitive tasks for 3 months lead to increased serum and tissue catabolic cytokines, with subsequent fibrosis and decreased bone formation, indicating that prolonged inflammation leads to tissue pathology. The underlying tissue changes, particularly the enhanced inflammatory response, were concomitant with sensorimotor functional declines as well as some declines in psychosocial abilities. We also noted that the tissue and serum inflammatory mediators responses are greater in aged rats than in young adult rats performing the same tasks, suggesting that prevention and interventions are of even greater importance in the aging worker.

D. PLANS. Now that our project is finished, we are completing our publication of this exciting work. We are expecting at least another 5 publications out of this work. Thank you very much for this exciting funding opportunity.

E. PUBLICATIONS:

Published Manuscripts:

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Barbe MF, Fedorcyzk J, Elliott MB, Amin M, Barr AE. Peripheral tendon and spinal cord neurochemical increases are induced in a model of repetitive motion injury with high force and high repetition exposure. Musculoskeletal and Neuronal Interaction international workshop, Germany, O36, May 10, 2008.

Elliott MB, Barr AE, Amin M, Barbe MF. Signs of central sensitization: inflammation induced by high demand task occurs in peripheral nerve and spinal cord tissue. Annual meeting of the Society for Neuroscience, 70.13, Nov, 2008.

Albrecht PJ, Rice FL, Barr AE, Barbe MF. Alterations in cutaneous innervation and epidermal chemistry following repetitive motion injury in rats. Annual meeting of the Society for Neuroscience, 154.6, Nov, 2008.

Varma D, Barbe M, Jansen-Varnum S. Quantitative correlation between lipid biomarkers and inflammatory proteins in Work- related musculoskeletal disorders (MSDs). Submitted to Pittcom conference for 2009.

INCLUSION OF GENDER AND MINORITY STUDY SUBJECTS:

Female Sprague-Dawley aged rats were utilized in this study.

INCLUSION OF CHILDREN:

Not applicable to this study using a vertebrate animal model.

MATERIALS MADE AVAILABLE TO OTHER INVESTIGATORS:

We have shared our model organism (tissues) with 6 different investigators at 2 institutions for examination of both epidermal neurological changes occurring as a consequence of performing repetitive tasks. These include Fayez Safadi, Steven Popoff and Judith Litvin at Temple University; and Phil Albrecht and a colleague at Albany, NY. Tissues were shared with Drs. Safadi, Popoff and Litvin for the investigation of cellular changes in bone as a result of repetitive task performance. Rats were shared with Dr. Albrecht for the study of epidermal innervation changes induced by nerve injury. Several publications and presentations have occurred and more are under way to report these findings to the public.

We welcome collaboration with the community of scientists interested in musculoskeletal and resulting neurological disorders in order to maximize use of research resources and to help avoid unnecessary duplication of facilities and procedures. The proposed research will result in several unique biological, equipment and procedural resources that could be readily shared with other investigators. These include 1) our rat model; 2) rat tissues exposed to high repetition task regimens; 3) the handle-pull apparatus, 4) the battery of behavioral tests of motor performance and function; and 5) the battery of tests for analysis of tissues and serum for markers of inflammation. These resources will be made available to other investigators as follows:

1) Animals/tissues: Live, exposed rats or harvested tissue samples from exposed rats will be made available for collaborative work in specific cases where 2 or more investigative teams will combine their unique expertise in such a way that the specific aims of the project proposed in our lab are not jeopardized. For example, we could transfer live animals to another lab for additional testing that will not disturb the forelimbs, and in which the forelimb tissues can be harvested for return to us. Such instances will be mutually agreed upon by the investigative teams using appropriate Material Transfer Agreements or Material Transfer Agreements for the Transfer of Organisms that specify that the animals/tissues will be used for research purposes only, State and Federal statutes regarding the care, use and handling of such specimens are adhered to by the recipient, the organisms/tissues will not be distributed to any third party, the recipient accepts responsibility for any liability incurred as a result of receiving, storing, using and disposing of the organism/tissue, and the source of the organism/tissue will be properly acknowledged in any reports or publications. Costs associated with the shipment of animals/tissues will be shared between our lab and the recipient lab(s) by prior agreement.

2) Equipment: Full descriptions of the handle-pull and NCV testing apparati have already been published in scientific journals (Barbe et al, 2003; Barr et al, 2003;Clark et al, 2003 and 2004). For investigators wishing to duplicate our equipment, we will provide technical support in the form of telephone and e-mail communications or hosting visits to our lab for consultation. We will provide at no cost vendor contact information for component instruments and supplies, operant testing chamber control macros written for MedPC software, reach data analysis macros written for MatLab data analysis programs written in Perl. We will also provide advice regarding the assembly and use of this equipment.

3) Procedures: We are able to conduct experiments on rat models or tissues from other laboratories to an extent that does not jeopardize progress on our proposed project and other projects in our lab. For example, we might examine tissues or serum for markers in a differently exposed rat model. We could examine human serum for markers of inflammation. We could perform behavioral tests in order to determine the presence of sickness behaviors in a differently exposed rat model. Any such opportunities would be under the auspices of appropriate Material Transfer Agreements as indicated in number 1) above and would be performed for no more than the cost of needed supplies and reagents.