Repetitive Stress Pathology: Soft Tissue

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Introduction

The purpose of this chapter is to integrate the basic science of injury, repair, and recovery with acute and chronic cumulative trauma disorders. The local cellular responses to repetitive forces are clearly outlined. Research findings based on animal models can explain the rise in the workplace incidence of repetitive strain injuries. Ergonomic adaptations and therapeutic interventions are discussed for the early stages of local tissue injury. However, peripheralization of the injury is not uncommon with continued excessive repetitive forces. The central consequences of overuse are highlighted based on laboratory and clinical science research. A clinical model of focal hand dystonia is used as example to support the hypothesis of aberrant central learning with chronic, excessive overuse of a limb. The chapter concludes by presenting evidence to support the effectiveness of complex learning based intervention strategies to remediate problems of chronic repetitive strain injuries.

Epidemiology and Management of Work-Related Musculoskeletal Disorders of the Hand and Wrist

The Problem

Work-related musculoskeletal disorders (MSDs), or work-related repetitive stress (overuse) injuries, have accounted for a significant proportion of work injuries and workers' compensation claims in Western industrialized nations since the late 1980s. The extent to which work is a causal factor in the development of such disorders is still the subject of much controversy. However, recent epidemiological studies have greatly improved methods of distinguishing between the contributions of workplace and nonworkplace risk factors in the development and severity of work-related MSDs. The evidence is clear that both workplace and nonworkplace factors can cause or exacerbate work-related MSDs, and the key to controlling the impact of such disorders in the workplace is prevention.

Although there is still much to learn about the underlying pathophysiology of these disorders, epidemiological research has provided information about the scope of the problem and likely causal factors that can be studied in the laboratory and among clinical populations. This section reviews the recent epidemiological literature on work-related MSDs of the hand and wrist, with an emphasis on the most prevalent peripheral nerve and musculotendinous disorders.

Definition of Work-Related Musculoskeletal Disorders and Trends in U.S. Industry

Definition of Work-Related Musculoskeletal Disorders

The U.S. Department of Labor defines work-related MSDs as injuries or disorders of the muscles, nerves, tendons, joints, cartilage, and spinal discs associated with exposure to risk factors in the workplace. Work related MSDs include sprains, strains, tears; back pain, hurt back; soreness, pain, hurt (except the back); carpal tunnel syndrome; hernia; or musculoskeletal system or connective tissue diseases and disorders, when the event or exposure leading to the injury or illness is bodily reaction/bending, climbing, crawling, reaching, twisting, overexertion, or repetition.[1] Work-related MSDs do not include disorders caused by slips, trips, falls, motor vehicle accidents or similar accidents; nor do they include Raynaud's phenomenon, tarsal tunnel syndrome, or herniated spinal discs. These cases are considered separately from musculoskeletal disorders in the Bureau of Labor Statistics Survey of Occupational Injuries and Illnesses.[1]

Work-Related Musculoskeletal Disorders

Work-related musculoskeletal disorders (MSDs) are injuries or disorders of:

- Muscles
- Nerves
- Tendons
- Joints
- Cartilage
- Spinal discs

Events or exposures that lead to work-related MSDs include:

- Bodily reaction/bending
- Climbing
- Crawling
- Reaching
- Twisting
- Overexertion
- Repetition

Work-related MSDs include:

- Sprains, strains, tears
- Back pain, hurt back
- Soreness, pain, hurt (except the back)
- Carpal tunnel syndrome
- Hernia
- Musculoskeletal system or connective tissue diseases and disorders

Work-related MSDs *do not* include:

- Disorders caused by slips, trips, falls, motor vehicle accidents, or similar accidents
- Raynaud's phenomenon
- Tarsal tunnel syndrome
- Herniated spinal discs

Risk Factors That Contribute to Work-Related Musculoskeletal Disorders

Physical and Biomechanical Risk Factors

- Repetitive movements
- Forceful movements
- Awkward or extreme postures
- Vibration
- Cold temperature

Psychosocial Risk Factors

- High work stress or demands
- Low job satisfaction
- Low decision control
- Poor workplace social support
- Contentious relationships with supervisors

Individual Predisposing Risk Factors

- Co-morbid medical conditions
- Physical and psychosocial risk factors not related to the workplace
- Obesity
- Age
- Female gender

Risk Factors for Work-Related Musculoskeletal Disorders

As the previously mentioned definition implies, certain risk factors are associated with the development or exacerbation of MSDs in the workplace. These risk factors include both physical or biomechanical and psychosocial conditions. In addition, certain worker characteristics may predispose individuals to being more severely affected by exposure to risk factors in the workplace.

Physical and Biomechanical Risk Factors. The physical or biomechanical risk factors that have been shown to contribute to the onset or exacerbation of work-related MSDs include the performance of highly repetitive and/or highly forceful motions; the assumption of fixed postures for long periods, particularly if such postures place joints in the extremes of physiological range of motion; the presence of vibration (e.g., during the operation of handheld power tools); and working in cold temperatures.[2,3] These risk factors may contribute individually or in combination. Some evidence indicates that a combination of physical risk factors, particularly repetitiveness and forcefulness, is more than additive in increasing the risk of peripheral neuropathy and musculotendinous disorders of the upper limb.[2,4,5]

Psychosocial Risk Factors. Psychosocial risk factors in the workplace also contribute to work-related MSDs. These factors are associated with levels of workplace stress, such as job content and demands, job control, and social support.[3] Examples of such factors include low worker control over work flow and organization (e.g., assembly line work); contentious relationships with co-workers and supervisors; low decision-making authority; time pressure; and, excessive employee performance evaluation by management.

Individual Predisposing Factors. Nonworkplace factors also can contribute to the development and exacerbation of work-related MSDs, and it is vital that health care providers explore such possibilities with workers receiving treatment for such disorders. These individual predisposing factors can include similar physical and psychosocial risk factors, such as playing a musical instrument or high levels of stress in the home. Certain past or current medical conditions also may be co-morbid risk factors for work-related MSDs.[3,6-8] Examples include past traumatic injury to the affected body part (e.g., a fracture or sprain) and systemic diseases that affect the musculoskeletal system (e.g., rheumatoid arthritis and other rheumatological disorders, diabetes mellitus, and diseases and disorders of the circulatory system). Women appear to be more susceptible to the

development of work-related MSDs than men, although this is highly industry dependent.[3,8-10] Advanced age may increase the impact of other risk factors on the severity of MSDs,[3,7,9] and obesity has been shown to predict the onset of MSDs.[11,12]

Work-related MSDs, therefore, have multifactorial causes, and the interaction between physical and nonphysical and workplace and nonworkplace risk factors is complex. This complexity contributes to the persistent controversy surrounding governmental regulation of these disorders. Consequently, private industry in the United States addresses these disorders on a voluntary basis, using industry-specific guidelines provided by the Occupational Safety and Health Administration (OSHA) (www.osha.gov).

Clinical Point

When treating patients with work-related MSDs, health care providers must bear in mind the complexity of causal factors and attempt to identify and address all of them in a comprehensive, holistic approach that emphasizes patient education.

U.S. Department of Labor Survey of Health Statistics

According to the most recent Bureau of Labor Statistics survey, work-related MSDs accounted for 435,180 (33%) lost workday injuries and illnesses in U.S. industry in 2003.[1] Repetitive motion (e.g., grasping tools, scanning groceries, and typing) was one of the most common events or exposures leading to work-related MSDs, and it accounted for the longest absences from work by exposure type (median of 22 lost days). The three occupational groups with the most work-related MSDs were (1) nursing aides, orderlies, and attendants (33,710 cases), (2) laborers and material movers (33,090 cases), and (3) truck drivers (20,580 cases). The first two groups involve jobs requiring heavy and repetitive lifting, whereas truck driving requires prolonged sitting with exposure to whole body vibration.

Work-related MSDs continue to cause substantial worker discomfort, disability, and loss of productivity. Among the remaining top 15 occupations reporting work-related MSDs were stock clerks and order fillers (repetitive moderate lifting and grasping), construction laborers (lifting and use of hand tools, some with vibration), and cashiers (repetitive light to moderate lifting and grasping). The service industries (e.g., health care) accounted for 71% of all MSDs, and goods-producing industries (e.g., manufacturing) accounted for the remaining 29%. Carpal tunnel syndrome was among the major disabling injuries and illnesses in 2003, and it had the highest median of lost workdays (32). Injuries to the wrist had a median of 17 lost workdays. These patterns of lost-workday injuries and illnesses show the impact of upper limb MSDs in the U.S. workforce.

Scope of Workplace Musculoskeletal Disorders in U.S. Industry

- One in three lost-workday injuries and illnesses is a work-related musculoskeletal disorder
- Work-related MSDs caused by repetitive motion had a median of 22 lost workdays
- Carpal tunnel syndrome has the highest number of lost workdays, a median of 32 days
- Wrist injuries have a median of 17 lost workdays

Epidemiological Evidence of Work-Related Repetitive Overuse Injuries of the Hand and Wrist

Two comprehensive reviews of the literature concerning work-related MSDs have been completed since 1997. A review undertaken by the National Institute for Occupational Safety and Health (NIOSH) included more than 600 epidemiological studies, dating from the 1970s to the mid-1990s, concerning work-related MSDs of the neck, upper extremity, and low back.[2] In this review, the framework for evaluating epidemiological evidence for a causal relationship between workplace risk factors and work-related MSDs included an evaluation of strength of association within studies, consistency across reviewed studies, temporality between exposure and work-related MSD outcome, evidence of an exposure-response relationship, and coherence of evidence. Based on this framework, evidence for a relationship between workplace risk factors and the development of work-related MSDs was classified into one of four categories: strong evidence of work-relatedness, evidence of work-relatedness, insufficient evidence of work-relatedness, and evidence of no effect of work factors.

The National Research Council (NRC) and the Institute of Medicine conducted a second, more exclusive review of the work-related MSD literature.[3] The NRC review included studies from the late 1970s to the late 1990s that examined tissue pathophysiology; mechanical, organizational, and psychosocial risk factors; and clinical interventions for work-related MSDs of the upper extremity and low back. For epidemiological studies of the upper extremity, the panel reviewed 42 studies of physical risk factors and 28 studies of psychosocial risk factors. These studies were selected from a larger candidate list of studies based on selection criteria that would allow the reporting or calculation of relative risk or attributable fraction, two epidemiological quantities used to estimate the effect of an exposure on the development of a health outcome.

For the purpose of this discussion, the findings of these two major reviews concerning the epidemiology of the most prevalent work-related hand and wrist disorders are summarized; those disorders are carpal tunnel syndrome and disorders of musculotendinous tissues.

Carpal Tunnel Syndrome

The NIOSH review reported strong evidence for a relationship between exposure to combinations of force and repetition or force and posture and the development of carpal tunnel syndrome (CTS). Evidence of a relationship between cumulative exposure to force, repetition, or hand/wrist vibration and CTS also was seen. The evidence was insufficient to determine the role of awkward postures alone in the development of CTS.

The NRC review included 15 studies of upper limb peripheral nerve disorders. Three studies reported an increased risk of CTS with exposure to high force alone.[4,13,14] Four studies reported an increased risk of sensory disturbances or CTS with exposure to vibration alone.[15-18] Four studies reported an increased risk of CTS with exposure to high repetition alone.[4,13,19,20] One study reported decreased nerve conduction velocity of the median nerve with exposure to a combination of repetitive motion and awkward posture.[21] One study reported an increased risk of CTS with exposure to cold temperatures.[19] Four studies reported an increased risk of CTS with exposure to various combinations of force, repetition, vibration, and cold temperatures.[4,13,19,20]

Musculotendinous Disorders

The NIOSH review reported that strong evidence existed that combinations of force and repetition were associated with the development of hand/wrist tendonitis. Evidence of a relationship between exposure to force, repetition, or awkward postures alone and hand/wrist tendonitis also was seen.

The NRC review included nine studies concerning musculotendinous disorders of the hand and wrist associated with exposure to physical risk factors. Five studies reported an increased risk of musculotendinous disorders with exposure to force alone.[4,22-27] Two studies found an association between exposure to vibration alone and musculotendinous disorders.[15,16] Two studies found an association between musculotendinous disorders and exposure to repetition alone[20] or to a combination of force and repetition.[4] Thirteen studies reported a positive association between psychosocial risk factors (e.g., job stress, job satisfaction, work demands) and hand and wrist discomfort or disorders.[4,28-39]

The overall conclusions of the NIOSH and NRC reviews, therefore, were essentially the same: evidence supports associations between workplace physical risk factors and hand and wrist work-related MSDs. The NRC study further examined the importance of psychosocial factors as contributors to the risk of hand and wrist MSD development. Both the NIOSH and NRC reviews identified gaps in the literature in the hope of guiding future research. In subsequent years, investigators began to address some of these issues, and a review of epidemiological studies from 1998 to 2003 concerning CTS and hand/wrist disorders recently was published.[40] Table 22-1 presents a more recent update of the epidemiological literature concerning CTS and hand/wrist musculotendinous disorders.

Epidemiological studies, many of them longitudinal rather than cross sectional, continue to support a causal relationship between prolonged exposure to highly repetitive and/or forceful hand-intensive tasks, vibration, psychosocial stress at work, and the development of CTS or other MSDs related to hand/wrist activities.[11,12,41-45] In addition, a past history of CTS or hand/wrist pain or discomfort increases an individual's risk of developing a new MSD related to upper limb activity or of exacerbating the existing activity-related MSD.[11,12,43,44]

Hours of computer mouse and keyboard use, as well as a history of computer use, are associated with an increased prevalence and incidence of upper limb discomfort and MSDs; however, controversy still exists in the literature concerning the magnitude and severity of computer-related MSDs.[44-48] MSDs related to upper limb activity have a higher prevalence and incidence in women,[45,48] and one author has shown that motherhood exacerbates this gender relationship by providing fewer opportunities for working mothers to relax and exercise outside of work.[49] Several investigators found an increased risk for work-related upper limb MSDs with increasing age and with a body mass index (BMI) near the borderline for obesity.[11,12,41,43]

The studies summarized in this chapter and those summarized in earlier reviews of the epidemiological literature support the contribution of physical and psychosocial risk factors at work to the development of upper limb MSDs. Studies also verify the multifactorial nature of these disorders and the role of nonworkplace risk factors and individual predisposing characteristics in their development. Clinicians need to be aware of all the factors that may have a bearing on the proper treatment of patients with work-related MSDs.

Management of Work-Related Musculoskeletal Disorders

Workplace Management

OSHA currently is developing industry-specific and task-specific ergonomic guidelines for voluntary use by U.S. employers.[50] Thus far, guidelines have been established for meatpacking plants,[51] nursing homes,[52] retail grocery stores[53] and poultry processing.[54] All of these guidelines embrace the same basic program components, which are set forth in the OSHA guidelines for nursing homes:

1. *Management support:* Clearly developed program goals, clearly identified program responsibilities for participants, adequate provision of resources, and oversight to ensure the success of the program.
2. *Employee involvement:* Early employee reporting of problems; also, employees provide insight (suggestions and evaluation) into work design issues and

Table 22-1

Summary of Recent Epidemiological Studies on Work-Related Carpal Tunnel Syndrome and Other Musculoskeletal Disorders of the Hand and Wrist

Authors (Country)	Sample	Study Design	Findings	Conclusions
Alexopoulos et al.[41] (Greece)	430 Dentists	Cross sectional survey of physical and psychosocial workload and complaints of musculoskeletal symptoms	Strenuous shoulder movements, use of vibrating tools, strenuous back postures, repetitive shoulder/hand movements, high perceived exertion, high need for recovery, and moderate perceived general health were associated with increased risk for hand/wrist complaints. Strenuous shoulder/hand movements were associated with increased risk of chronicity and absenteeism. Chronicity increased with age.	Physical load among dentists places them at risk for MSDs. Psychosocial factors, such as perceived health status and perceived exertion, are associated with more severe complaints and absenteeism.
Bovenzi et al.[42] (Italy)	159 Forestry workers and 146 manual laborer controls	Cross sectional, control group design to determine prevalence of vibration-induced white finger, CTS, and soft tissue disorders	Forestry workers showed increased prevalence of peripheral sensorineural disturbances, soft tissue disorders of the upper limbs, and CTS compared to controls. Increased vibration exposure, through the use of chain saws, and increased years of tool use among forestry workers were associated with peripheral neuropathies.	Exposure of forestry workers to a combination of risk factors (segmental vibration, forcefulness, and awkward postures) is associated with the occurrence of peripheral neuropathies and soft tissue disorders of the upper limb.
Gell et al.[43] (United States)	432 Industrial and clerical workers with no history of carpal tunnel syndrome	Longitudinal study over 5.4 years to develop a predictive model for work-related CTS	Average incidence rate of CTS was 1.2% per year. Multiple regression indicated that workers with baseline numbness, tingling, burning and/or pain in the fingers were 5.2 times more likely to develop CTS. For each 0.1 msec increase in median-ulnar peak latency, the relative risk for developing CTS increased 29%. Risk of CTS tended to risk with increased BMI and high risk hand threshold limit values established by the ACGIH.	Incidence rate in this population was higher than in the general population. This study corroborated findings from earlier cross sectional studies; the findings indicated that early symptoms may be predictors of future CTS and that these workers therefore are logical targets for preventive intervention.

Hamilton et al.[46] (United States)	111 Female college students (72 respondents)	Cross sectional study to determine prevalence of computer-related musculoskeletal complaints and their association with hours of use, laptop use, and job strain	Eighty-one percent of respondents reported computer-related musculoskeletal complaints. None of the factors examined were statistically associated with those complaints. Although not statistically significant, 90% of respondents using a laptop computer reported musculoskeletal complaints.	Most students reported computer-related musculoskeletal discomfort. Future studies should include more diverse student populations.
Jensen[44] (Denmark)	2576 Employees who use computers	Longitudinal study to determine risk factors for musculoskeletal symptoms in the neck and hand/wrist	Hand/wrist symptoms were predicted by previous symptoms at baseline and low influence at work for both men and women and by sensorial demands for women only. Almost continual or continual computer use was associated with increased hand/wrist symptoms.	Early intervention for reported hand/wrist symptoms can reduce persistent or recurrent symptoms. Psychosocial issues at work contribute to hand/wrist symptoms. Limiting computer use to less than 0.75 of the workday can help prevent hand/wrist symptoms.
Kryger et al.[45] (Denmark)	6943 Participants from public and private workplaces	Longitudinal study to determine prevalence and incidence of forearm pain, signs of tenderness and nerve entrapment, and association with computer work, physical workplace factors, and psychosocial factors	The 1-year incidence of self-reported forearm pain was 1.3%. Increased risk of new forearm pain was associated with more than 30 hours/week of mouse use and more than 15 hours/week of keyboard use. High job demands and time pressure at baseline increased the risk of new forearm pain. Women had a twofold increased risk of developing forearm pain.	Intensive mouse use and keyboard use were the main risk factors for forearm pain, but the overall incidence was low; therefore these activities cannot be considered severe occupational hazards.
Larsson et al.[134] (Denmark)	6943 Participants from public and private workplaces	Longitudinal study to determine relationship between computer work and elbow and wrist/hand pain, conditions, and disorders (only wrist/hand findings reported in this table)	The duration of mouse use and the duration of keyboard use were significantly associated with wrist/hand pain, and keyboard exposure showed a threshold effect with 12-month wrist/hand pain at 1-year follow-up. Clinical diagnoses on physical examination were not associated with mouse or keyboard exposure.	Self-reported, low force exposures of mouse and keyboard time predicted wrist/hand pain but were not predictors of clinical conditions on physical examination.

(Continued)

Table 22-1
Summary of Recent Epidemiological Studies on Work-Related Carpal Tunnel Syndrome and Other Musculoskeletal Disorders of the Hand and Wrist—Cont'd

Authors (Country)	Sample	Study Design	Findings	Conclusions
Schlossberg et al.[48] (United States)	206 Electrical engineering and computer science graduate students at a large public university	Cross sectional determination of persistent or recurring UE and neck pain associated with computer use	Sixty percent of the participants reported UE or neck pain attributed to computer use. Logistic regression showed that pain was significantly associated with female gender, years of computer use, and hours of computer use per week.	Prevalence of UE pain is high among students who make heavy use of computers, which suggests a need to identify interventions to reduce symptom severity and prevent impairment.
Strazdins and Bammer[49] (Australia)	737 Public service employees (73% clerical)	Cross sectional determination of upper body musculoskeletal symptoms in relation to workplace and nonworkplace risk factors	Eighty-one percent reported some symptoms; of these, 20% reported severe and continuous symptoms. Prevalence was higher among females. Parenthood (i.e., motherhood) exacerbated the gender differences in prevalence.	Gender differences can be explained by additional risk factors to which women are exposed outside of work (i.e., in relation to domestic duties). For example, women who were mothers reported less opportunity to relax and exercise outside of work compared to men.
Wellman et al.[306] (United States)	1901 Work-related CTS cases from 1992-1997	Cross sectional survey of CTS cases to determine industry, occupation, attributed source of work-related CTS, outcomes, and employer intervention practices	Leading attributable sources were office and business machinery (42%) and hand tools (20%). Managers and professional specialty workers were up to four times more likely to report employer interventions and equipment/work environment changes than were higher risk groups.	New cases of work-related CTS are likely in high risk industries. Employees with CTS in high risk industries are less likely to be provided with employer-implemented primary prevention measures compared to lower risk workers.
Werner et al.[11] (United States)	501 Industrial and clerical workers with a history of no or mild UE discomfort	Longitudinal study over 5.4 years to determine predictors of new onset of UE pain or discomfort	Predictors of new onset or progression of UE pain/discomfort were a BMI over 28, age over 40 years, mild pain/discomfort at baseline, combination of hand repetition and force in the borderline or high risk hand threshold limit values as established by the ACGIH.	Both ergonomic and personal health factors contributed to UE pain and discomfort. Prevention strategies should address all sources of risk.
Werner et al.[12] (United States)	501 Industrial and clerical workers with no history of shoulder, elbow, wrist, or hand tendonitis at baseline	Longitudinal study over 5.4 years to determine predictors of new cases of UE tendonitis	Predictors of new cases of UE tendonitis (shoulder, elbow, wrist, and hand) were a BMI over 30, age over 40 years, neck or shoulder discomfort at baseline, a history of CTS, discomfort rating at baseline, and an increased average shoulder posture rating.	Both ergonomic and personal health factors contributed to UE tendonitis. Prevention strategies should address all sources of risk.

ACGIH, American Congress of Governmental Industrial Hygienists; *BMI*, body mass index; *CTS*, carpal tunnel syndrome; *MSD*, musculoskeletal disorder; *UE*, upper extremity.

solutions and share responsibility for program development and implementation.
3. *Problem identification:* Systematic procedures using various sources of information, such as OSHA injury and illness logs, data from workers' compensation claims, and surveillance and workplace analysis.
4. *Solution implementation:* Typically involves changes to eliminate or reduce workplace hazards or problematic work practices, or both.
5. *Injury management:* Emphasizes early detection and intervention.
6. *Training of employees and managers:* Training in the risks and detection of MSDs and the procedures required to respond to an MSD incident.
7. *Regular program evaluation:* Determination of quantifiable measures, such as number and severity of MSDs.[52]

The success of such workplace MSD management programs relies on clear communication between workers, managers, and health care providers. Such communication requires an atmosphere of cooperation and mutual trust among all stakeholders. One benefit of establishing such a program is that it often alleviates the impact of psychosocial risk factors by providing employees with an opportunity to contribute directly as members of a cohesive MSD management team.

Essential Components of a Workplace Management Program for Musculoskeletal Disorders

- Management support
- Employee involvement
- Problem identification
- Solution implementation
- Injury management
- Training of employees and managers
- Regular program evaluation

Clinical Management

The biopsychosocial model of clinical management has been clearly demonstrated to be the most successful approach to the management of activity-related MSDs. In this model, the interactions of physical impairments, personal psychological factors, and psychosocial factors are recognized and targeted for treatment in a holistic approach to care.[55] Biopsychosocial management programs have several advantages:

1. They emphasize the importance of using a multidisciplinary health care team to address the multiple causal factors of an activity-related MSD.
2. They illustrate the need for clear communication and cooperation between health care providers, injured workers, and various stakeholders in the workplace.
3. They show that clear communication is greatly enhanced by trained case managers who oversee all aspects of health care and workplace management.
4. They demonstrate that effective health care interventions for activity-related MSDs do not necessarily result in a cure; rather, they lead to long-term worker- and workplace-focused management through effective problem solving by the entire MSD management team.

It is beyond the scope of this chapter to describe in detail such MSD clinical management programs; however, several recent examples in the literature can guide the reader.[56-58]

Essential Components of a Clinical Management Program for Musculoskeletal Disorders

- Holistic approach to care with focus on physical impairments and personal and workplace psychosocial factors
- Multidisciplinary health care team
- Communication and cooperation between health care providers, injured workers, and the workplace
- Trained case managers
- Long-term worker- and workplace-focused management

Summary

Activity-related MSDs account for one in three lost-worktime injuries and illnesses in U.S. industry. Repetitive motion tasks (e.g., grasping tools, scanning groceries, and typing) were among the most frequent events or exposures leading to work-related MSDs in 2003; they also accounted for the longest absences from work by exposure type (median of 22 lost days). These disorders have a major impact on workers' compensation costs, absenteeism, and loss of productivity.

Strong epidemiological evidence indicates that risk factors for the development of work-related MSDs of the upper limb include the performance of hand-intensive tasks in a manner that is highly repetitive or forceful (or both) in awkward or sustained postures, with or without vibration and cold temperatures.

Psychosocial stress also increases the risk of work-related MSDs of the upper limb. Individual predisposing factors that contribute to the risk of upper limb, work-related MSDs include past or present co-morbid medical conditions, female gender, obesity, and advanced age.

The necessary components of an effective workplace management program for MSDs are (1) management support, (2) employee involvement, (3) problem identification, (4) solution implementation, (5) injury management, (6) training of employees and managers; and (7) regular program evaluation. Effective clinical management of work-related MSDs should follow a biopsychosocial model

that emphasizes communication among the affected worker, workplace personnel, and the health care provider.

Much has yet to be learned about the underlying pathophysiology of work-related MSDs. The sections that follow discuss some recent findings in both animal models and clinical populations that have enhanced our understanding of the relationship between repetitive motion and tissue pathophysiology and movement dysfunction, as well as a novel treatment approach based on these findings.

Pathophysiology of Activity-Related Neural and Musculotendinous Disorders

The Problem

Musculoskeletal disorders related to overuse have been associated with a number of changes in neural, muscular, tendinous, and bony tissues. The following sections review the processes of inflammation and wound healing and factors that affect those processes. Then, current evidence for neural, muscular, and tendinous pathophysiological changes in the development of overuse injuries is presented, as well as possible mechanisms for those changes. A conceptual model for changes in tissue tolerance, with continued tissue loading, that affect inflammation and healing also is presented.

Review of Wound Healing and Its Relationship to Overuse Injuries

Wound healing is the process by which tissues attempt to restore normal tissue architecture and function after injury in an effort to restore homeostasis. A complex series of molecular, vascular, and cellular responses are initiated the moment a tissue is injured. Wound healing involves four distinct phases, which develop in an orderly but overlapping manner: hemostasis, acute inflammation, proliferation/fibroplasia, and remodeling/maturation.[59,60]

Unfortunately, many factors affect wound healing. For example, if the injury or initiating stimulus is repetitive or chronic, the tissues have little chance to complete the healing process, and either chronic inflammation or fibrosis can result. In these cases, chronic or regular release of a variety of inflammatory or fibrogenic biochemical mediators can perpetuate the inflammatory response or cause excessive proliferation and fibroplasia. Some of these same mediators are cytotoxic at high levels. The patient's overall health also must be considered in wound healing. Many metabolic disorders, such as diabetes, can directly affect the success of wound healing, and these disorders therefore must be considered co-morbidities when a treatment plan is designed.[6]

Acute Inflammatory Response

Hemostasis (clotting) and acute inflammation is the tissue's initial response to acute injury or infection. The hemostasis response causes the wound to be closed by clotting, which occurs through platelet activation. The acute inflammatory response is characterized by infiltration of immune cells and fluid; it typically lasts 24 to 48 hours and usually is complete in 2 weeks. It is characterized by the cardinal signs of inflammation, which are redness (rubor), swelling (tumor), heat (calor), and pain (dolor). The first three signs are due to the vascular reactions of vasodilation and increased permeability.[61]

Acute Inflammation

- Vascular reaction
- Cellular reaction (infiltration of platelets, neutrophils, macrophages, and/or lymphocytes)

Vascular Reaction. An initial transient arteriolar constriction is followed by vasodilation, increased endothelial cell permeability, exudation of fluid, and transmigration of blood cells into tissues. Vasodilation gives rise to the classic signs of redness and heat, whereas exudation and cell infiltration lead to tissue edema and swelling. The pain (dolor) associated with inflammation usually is due to increased pressure on nerves caused by edema. Biochemical mediators, such as histamine, prostaglandin, bradykinin, serotonin, and cytokines (including tumor necrosis factor-1 [TNF-1] and interleukin-1 [IL-1]), play crucial roles in the process of vasodilation.[61] The vascular reaction is summarized in Figure 22-1.

Cellular Reaction. The migration of cells into the interstitial space is a process called *chemotaxis*. The type of cells that infiltrate depends on the type of stimulus (i.e., injury, infectious, or allergic) and the specific molecules and inflammatory mediators released by the injured cells and tissues. Critical players in this reaction are platelets and leukocytes (including neutrophils, monocytes/macrophages, and lymphocytes; see Figure 22-1). The recruitment of leukocytes involves specific interactions with endothelial cells that promote the processes of rolling, activation, arrest, adhesion, and migration.

Platelets are anuclear, cytoplasmic fragments derived from megakaryocytes.[62] They are more numerous than leukocytes (discussed later) and the first repair components to appear when a wound is created.[63] Their primary function is to initiate the coagulation cascade and form the fibrin plug that fills the tissue gap, a process called *hemostasis*. Platelets also release a variety of growth factors and cytokines upon contact with collagen and other extracellular matrix components. They release platelet-derived growth factor (PDGF), which initiates the healing cascade by being chemotactic to neutrophils and monocytes and by inducing the proliferation of fibroblasts.[63]

Platelets release many other proteins, including transforming growth factor beta (TGF-β) and proinflammatory

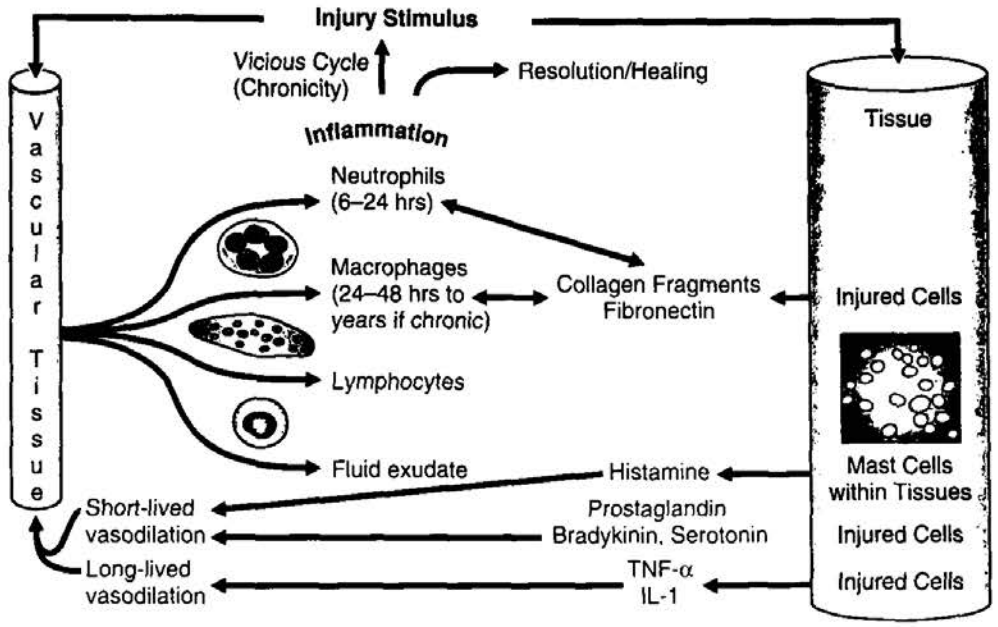


Figure 22-1

Sequence of events in acute inflammation in response to a mechanical injury stimulus. Mechanical injury can damage vascular, neural, and musculoskeletal tissues and lead to the mobilization of leukocytes, neutrophils and macrophages by circulatory distribution and/or by chemotaxis induced by the presence of collagen fragments and fibronectin at the injury site. Even when the vasculature is spared mechanical injury, the release of inflammatory mediators from tissue mast cells and injured cells causes vasodilation and leukocyte mobilization. Ideally, acute inflammation resolves and injured tissue heals either completely or with the formation of a fibrous scar. With a persistent injury stimulus or severe tissue disruption, the inflammatory response itself may cause further injury and inflammation, thereby setting up a vicious cycle with subsequent incomplete healing and/or chronic inflammation. *TNF-α*, Tumor necrosis factor alpha; *IL-1*, interleukin 1. (Modified from Barr AE, Barbe MF: Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders, *J Electromyogr Kinesiol* 14:79, 2004.)

cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α). These proteins are involved in re-epithelialization and tissue healing through their ability to induce collagen and fibronectin production by fibroblasts.[64,65] However, they are also key mediators of inflammation.

Neutrophils are the first leukocytes to be chemotactically drawn to the wound site. Neutrophils are mature white blood cells of the granulocyte series (i.e., they contain cytoplasmic granules), and they constitute 54% to 56% of leukocytes.[61] They typically appear within 1 hour after the wound occurs and peak between 24 and 48 hours after an injury.[66,67] Neutrophil infiltration is associated with secondary tissue damage in overloaded muscles because neutrophils release lytic enzymes and produce superoxide free radicals.[67,68] These free radicals, which are antimicrobial, break down injured cells and tissues by disrupting cell membranes, denaturing proteins, and disrupting cell chromosomes.[69] Neutrophils also produce proteinases for debridement and proinflammatory cytokines (e.g., TNF-α),[66] which perpetuates the inflammatory response by attracting macrophages and other immune cells. Finally, neutrophils are short-lived, a characteristic attributable to a process of genetically programmed cell death known as *apoptosis.*

In contrast to neutrophils, macrophages are a heterogeneous group of long-lived cells with a myriad of functions. Macrophages derive from circulating monocytic leukocytes (monocytes), which convert into ameboid, phagocytic cells known as *macrophages* as they invade injured cells and tissues. These cells are voraciously phagocytic and can live for months or years migrating into and out of tissues. They break down necrosed muscle, dead neutrophils, and cell debris through the release of proteolytic enzymes (e.g., collagenase, elastase, and plasminogen activator). Also, during phagocytosis they release numerous potentially cytotoxic compounds, including reactive oxygen species and nitric oxide, which can contribute directly to further tissue injury[70] (i.e., secondary tissue injury). Furthermore, activated macrophages secrete additional PDGF and proinflammatory cytokines, and the latter are key mediators of inflammation.[59,71]

Macrophages, particularly the ED2 subset (i.e., resident macrophages), also perform wound healing functions through their secretion of growth factors (e.g., TGF-β), which stimulate the proliferation of many cell types, leading to tissue repair and healing. In addition, macrophages secrete anti-inflammatory cytokines (e.g., IL-10), which downregulate the production of proinflammatory mediators.[72,73] Macrophages also secrete angiogenic-promoting

factors, which initiate migration of endothelial cells and the growth of new capillaries into the wound site.[74]

Lymphocytes are a third line of leukocytes. They are agranular and are divided into two main subsets, T cells (thymus derived) and B cells (plasma or memory cells that are not thymus dependent). T cells typically arrive 5 days after injury and peak by day 7.[65] They are long-lived cells (months to years) that typically are not seen during acute inflammation; rather, they are more prominent in chronic conditions.[75] T lymphocytes mediate the delayed immune response (cell mediated) by regulating B-lymphocyte and macrophage phagocytic functions.[63] In contrast, B lymphocytes are short-lived and do not play a role in cell-mediated immunity. Instead, they transform into antibody-producing plasma or memory B cells, and through the release of various cytokines (e.g., interferon gamma [IF-γ], IL-2, and TGF-β), they enhance macrophage function.[65] Lymphocytes are not required for the initiation of wound healing, but they are essential for normal repair because they secrete lymphokines, including TGF-β, TNF-α, and fibroblast-activating factor (FAF), all of which induce the proliferation of fibroblasts. However, high concentrations of these lymphokines, particularly TNF-α, are cytotoxic to fibroblasts and other cells.[65,76] Long-term continuation of an acute inflammatory response (i.e., chronic inflammation) can lead to cytotoxicity or fibrosis, and the latter is associated with excessive stimulation of fibroblast proliferation and collagen production.[59,77]

Repair Phase of Wound Healing Versus Chronic Inflammation and Fibrosis

Healing and Repair. The process of wound healing is an effort to restore normal tissue function and architecture after injury. Essentially, three primary outcomes are possible with tissue injury: (1) complete resolution with total restoration of normal tissue structure; (2) repair with scar formation of varying degrees, depending on the level of injury; and (3) chronic inflammation. *Complete restoration* is the regeneration or recreation of the tissue to a state in which it may even be in a better form or condition than before the injury. *Repair* is the process of mending tissue after decay or damage. The mended area may not be complete but may consist of a collagenous scar that fills the damaged tissue region. Substantial tissue injury may also occur in tissues with little capacity for regeneration (e.g., skeletal muscle and nerve) or after prolonged edema. The edematous tissue, injury site, or tissue gap then fills with exudate, immune cells, and fibroblasts before converting to fibrotic connective tissue,[60,78,80] which is later remodeled, albeit slowly.[81] In the case of tendons, a fibrotic scar also fills the tissue gap.[60,79] However, with tendons, although remodeling of the scar area occurs, the tendon never returns to normal structural or biomechanical properties, even after long periods of recovery.[79]

Phases of Wound Healing

Repair Phase
- Infiltration of immune cells to clear debris
- Fibroplasia (increased fibroblast proliferation and matrix production)
- Angiogenesis (increased migration and proliferation of endothelial cells)
  - Increase in capillary beds in wound site
- Re-epithelialization of skin or mucous membrane
- Scar formation

Remodeling Phase
- Remodeling and maturation of tissue toward normal, preinjury structure
  - Collagen conversion: Type III (first to be deposited) to type I
  - Realignment of fibroblasts in wound

The repair phase begins once the wound site has been cleared of debris, a process that occurs during the acute inflammatory phase of wound healing. The repair phase consists of a proliferation/fibroplasia phase and a remodeling/maturation phase (Figure 22-2).[60] The proliferative phase is characterized by the migration into the injury site of fibroblasts, which proliferate to fill in the wound site. This phase is also called the *granulation tissue formation phase*, because microscopically the wound site appears to be filled with many small immune cells and proliferating fibroblasts. The primary function of fibroblasts is to produce new intracellular and extracellular matrix, such as collagen type III.

The remodeling/maturation phase of repair and healing is characterized by collagen conversion, wound contraction, and scar formation.[59] Collagen type III gradually converts to collagen type I, the collagen becomes cross-linked, and fibroblasts realign along the axis of force through the tissue.[59,60] Unfortunately, some tissues, such as tendons, rarely recover fully to their original structure and strength.

Chronic Inflammation and Fibrosis. Instead of resolving, an acute inflammatory response may be prolonged chronically. Chronic inflammation (sometimes referred to as chronicity) can be considered an interruption of the normal healing progression and can last for months or years. It is associated with certain conditions that prolong the inflammatory response because of chronic exposure to the initiating stimulus or because of a smoldering subacute inflammation or infection. Chronic inflammation is characterized by the prolonged presence of large numbers of macrophages in and around tissues, which contribute to secondary tissue damage through their prolonged phagocytic activity and release of cytotoxic free radicals. Chronic production of inflammatory mediators, such as cytokines,

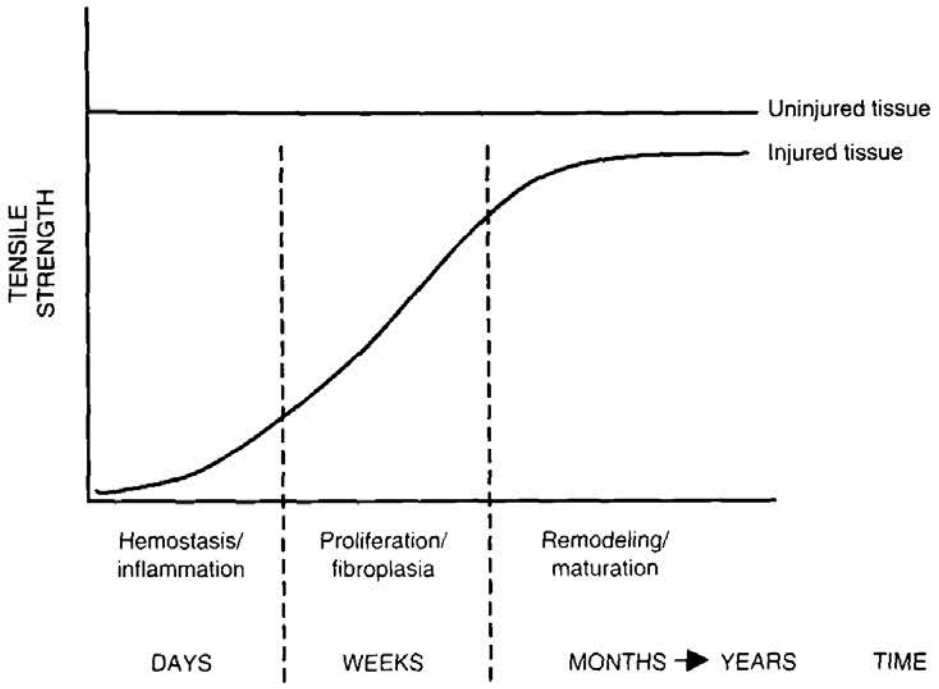


Figure 22-2
Wound healing response in tendons. (From Lin TW, Cardenas L, Soslowsky LJ: Biomechanics of tendon injury and repair, *J Biomech* 37:866, 2004.)

by the macrophages and by cells that are either injured, irritated, or apoptotic can perpetuate the inflammatory cycle, because these molecules are chemotactic for additional immune cells. Cytokines are also fibrogenic mediators, as are connective tissue growth factor (CTGF) and TGF-β. Overproduction or chronic production of fibrogenic mediators can lead to excessive activation of fibroblasts and excessive matrix deposition in and around the wound site, a process called *fibrosis*. Studies now support the hypothesis that chronic inflammation generally precedes fibrosis.[82,83] These same inflammatory and fibrogenic mediators can enter the bloodstream, circulate, and stimulate systemic inflammatory effects, widespread secondary tissue damage, and widespread fibrosis in healthy tissues.[40,77,84]

Chronic Inflammation

- Perpetuation of inflammatory response
  - Continued presence and activity of macrophages in wound site
  - Continued production of inflammatory mediators by cells in wound site
- Fibrosis
- Either or both of these two components may become widespread or systemic

Factors That Affect Wound Healing

Many diverse factors affect wound healing, including ischemia, scar formation, malnutrition, infection, and stress. Circulating cytokines (discussed previously) can induce bone formation, degradation of cartilage and other connective tissues, and recruitment of leukocytes into widespread tissues areas. Invading neutrophils and macrophages lead to secondary tissue damage through phagocytosis, free radical damage, and tissue and protein catabolism. These cells often invade not only the injury site but also nearby healthy tissue and degrade that tissue as well. The overall health of the tissues and of the individual are also key factors in the end success of wound healing.[6]

Other factors in the success of wound healing are neurogenic in origin and arise from a family of biochemical mediators known as *neuropeptides*. Neuropeptides are secreted by autonomic efferent, nociceptive afferent fibers and perivascular terminals of noradrenergic and cholinergic fibers. They have been shown to play a role in all phases of the healing response. Table 22-2 summarizes the primary effects of several of these neuropeptides during wound healing.

Table 22-2
Neuropeptides Involved in Wound Healing

Neuropeptide	Role in Wound Healing
Substance P	Upregulates endothelial cell receptors that promote leukocyte adhesion and migration; chemotactic for neutrophils and macrophages[101-103]
Catecholamines	Impair T-lymphocyte production and neutrophil phagocytic activity[65]
Glucocorticoids	Impair T-lymphocyte production and neutrophil phagocytic activity[65]

Changes in Tissue Tolerance with Continued Tissue Loading

The authors' work and that of others lends credence to the theory that overexertion is an initiating and a propagating injury stimulus in work-related MSDs and overuse injuries. The authors have speculated that the mechanisms leading to tissue repair are prevented by the continued cycle of tissue trauma in repetitive motion injury.[84,85] Although cumulative loading of viscoelastic tissues in the short term may increase the likelihood that applied loads will result in tissue injury, it is nonetheless an overexertion event that initiates a cyclical and perhaps persistent inflammatory response. Phagocytic cell infiltration, an increase in the number of free radicals, and induction of inflammatory cytokines by persistent injury and inflammation can lead to tissue degeneration, such as tissue necrosis, pathological tissue reorganization, and subsequent biomechanical failure. Repeated bouts of injury, inflammation, and fibrosis eventually contribute to decreasing tissue tolerance over time, such that lower levels of exertion lead to tissue damage, which further reduces tissue tolerance and functional performance. Thus a vicious cycle of injury leading to long-term functional disability is established. Figure 22-3 presents a schematic of this dose-dependent decline in tissue tolerance.

Such decreasing tissue tolerance may explain why analyses of human tissue, such as the flexor tendon synovium in CTS and the extensor carpi radialis brevis tendon in lateral epicondylitis, do not reveal acute inflammatory indicators but instead show tissue degeneration, fibrosis, and/or necrosis.[74,86-89] These patient populations are tested long after the acute inflammation has resolved. The authors agree that designating such soft tissue injuries as noninflammatory informs clinicians of effective treatments for patients seen so late in the process; however, they disagree that the early pathomechanical initiator of these conditions is noninflammatory. The mere presence of fibrotic tissues and anti-inflammatory mediators in the tissues of patients with overuse injuries strongly suggests earlier proinflammatory episodes.

Evidence of Peripheral and Central Neural Changes in the Development of Overuse Injuries

Nerve damage can be caused in numerous ways. Typical modes of injury include compression, overstretching, contusion, and frank tears. Compression and overstretching are the most common types of nerve damage associated with repetitive motion.[78,90-92] However, several other

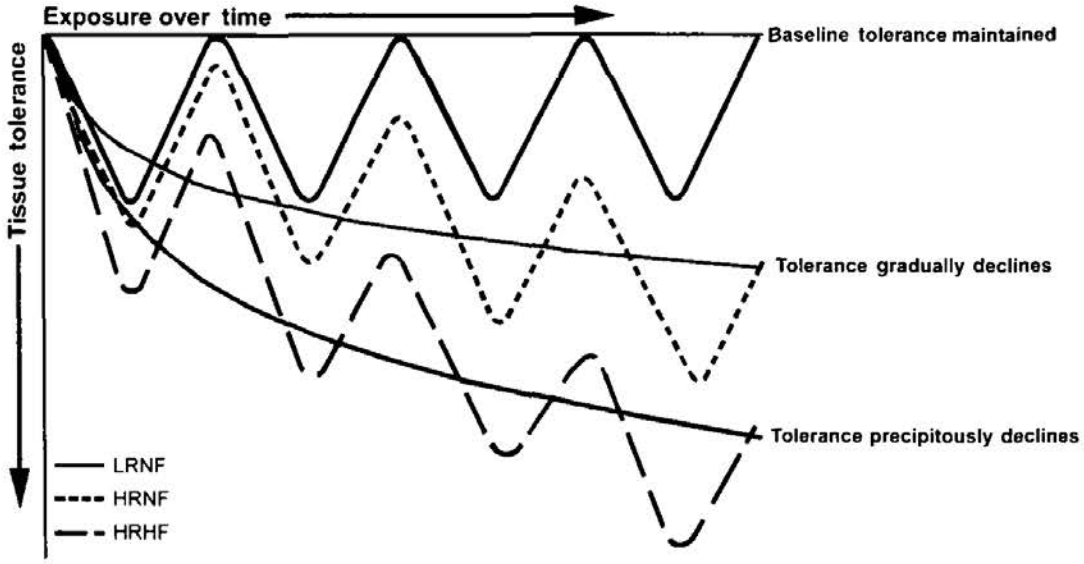


Figure 22-3

Conceptual model of the hypothesized long-term effects of repeated tissue inflammation on tissue tolerance and underlying mechanisms of tissue responses. This model is consistent with the overexertion theory of the development of work-related musculoskeletal disorders. If tissue exposure levels stay below a critical threshold, inflammation resolves (indicated by the episodic fluctuations of tissue tolerance) and adaptive remodeling to the task occurs (indicated by the return to baseline tissue tolerance of the upper low repetition, low force [LRLF] curve between the inflammatory episodes). When tissue exposure exceeds a critical threshold, incomplete healing results (indicated by the lower two curves); exposure dependent declines in tissue tolerance lead to persistent injury and inflammation followed by tissue disorganization, degeneration, or cell death. Depending on the degree of exertion, this decline in tissue tolerance may be gradual (as in the high repetition, low force [HRLF] group) or precipitous (as in the high repetition, high force [HRHF] group). In addition to the overall decline in tissue tolerance, inflammatory episodes result in transient periods of even lower tissue tolerance, resulting in the fluctuations in tissue tolerance shown. Modification of the tissue exposure level during these transient tissue tolerance episodes may have an important impact on the maximization of tissue tolerance. Furthermore, motor function declines with increasing task demands. (From Barr AE, Barbe MF: Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders, *J Electromyogr Kinesiol* 14:83, 2004.)

modes of nerve injury are not exclusive to overuse injuries; these include transection (cutting), crushing mechanisms, immunological causes (creating a chronic autoimmune response in the nerve), chronic constriction injury, and vascular disease. Each of these types of injuries can be a compounding factor in a patient with overuse injuries.

Clinical, Histological, and Biochemical Signs of Nerve Injury

Clinical signs of nerve damage include acute pain, chronic pain, loss of sensation and discrimination, declines in nerve conduction velocity, and motor dysfunction. Examples of motor dysfunction include weakness, atrophy, or paralysis of a muscle. Abnormal sensations, such as hyperalgesia (i.e., hypersensitivity) and mechanical allodynia (i.e., nonnoxious pain), may also develop.

Clinical Signs of Nerve Damage

- Acute pain
- Chronic pain state
- Loss of sensation and discrimination
- Reduced nerve conduction velocity
- Motor dysfunction (weakness, atrophy, or paralysis)

Mechanical disruption of axons and myelin leads to histological signs of nerve damage, such as myelin degradation, Schwann's cell necrosis, and axon degeneration. Macrophage infiltration also occurs as a result of disruption of the blood-nerve barrier or injury-induced chemotaxis, or both. The macrophages then add to the loss of Schwann's cells and axons by phagocytosing even partly injured cells in an effort to debride the injury site and stimulate repair. Each of these histological changes contributes to the decline in nerve conduction by disrupting the flow of current that would occur after loss of the Schwann cell's myelin sheath or by interfering with axoplasmic flow that would occur after disruption of the axons. Nerve compression, edema, and chronic inflammation also lead to the development of fibrotic tissue in extraneural and intraneural tissues,[78,80,91,93-95] which further contributes to nerve compression if the fibrosed area lies within a constrained space, such as the carpal tunnel.

Biochemical signs of peripheral nerve damage include increased production and release of a variety of mediators of pain, inflammation, and vasodilation by Schwann's cells, infiltrating macrophages and mast cells, and the nerve terminal itself. For example, IL-1, TNF-α, and IL-6 are increased after nerve injury and contribute to further inflammation by recruiting macrophages intraneurally. These same cytokines also enhance pain by sensitizing nociceptors through the activation of the neuron or by lowering the threshold for firing in the larger nerve trunk or surrounding tissues. Increased intraneural levels of cytokines also contribute to hyperalgesia and mechanical allodynia.[96-100] Schwann's cells also produce bradykinin, which results in vasodilation, and the nerve terminals produce substance P (SP), vasoactive intestinal peptide (VIP), and calcitonin gene–reactive protein (CGRP), which contribute to immune cell infiltration of intraneural tissues and further sensitization of the nociceptors.[65,101-103]

Peripheral Nerve Trauma Associated with Repetitive Tasks

In work-related MSDs, the primary causes of peripheral nerve trauma are overstretching, increased intracarpal pressure with compression of nerves during flexion or extension or fingertip loading, and overstretching of neuronal tissues during excursion.[90,92,104,105] Experimentally induced nerve compression has been used to determine the pathophysiological effects of compression on nerve tissues (Table 22-3). Such experiments found clear signs of demyelination in a rabbit tibial nerve by 3 weeks after a 2-hour increase of pressure to 200 and 400 mm Hg.[106] In a rat model, demyelination and Schwann's cell death were present in the sciatic nerve by 7 days after an acute increase of pressure to 30 mm Hg.[107]

Animal models of chronic nerve constriction injury using cuff banding or suture ligatures have shown that chronic compression leads to an upregulation of inflammatory cytokines intraneurally, intraneural and extraneural fibrosis (i.e., increases in collagen matrix in and around the nerve), Schwann's cell death, and axonal demyelination and degradation.[80,93,94,96,99,108] These pathological nerve changes lead to loss of electrophysiological function (i.e., decreased nerve conduction).[80,93] Mechanical allodynia and hyperalgesia (discussed later) also were associated with chronic nerve constriction.[96,99,108]

The authors' laboratory has investigated the pathophysiology of repetitive motion injuries of the upper limb caused by voluntary high repetition tasks with or without force.[40,71,78,84,85,91,109-114] The authors have developed an innovative rat model of voluntary repetitive and forceful reaching to answer fundamental questions about the effects of such tasks on musculoskeletal tissues. A force training apparatus was designed in which rats can perform at a range of reach rates and force levels. The apparatus was used to determine the short-term effects (up to 12 weeks) on sensorimotor behavior and the pathophysiological outcomes of forelimb tissues that occurred with (1) a voluntary low force task (less than 15% of maximum grip strength) performed at low frequency reach rates (low repetitions, low force [LRLF], 2 reaches/min) and high frequency reach rates (high repetitions, low force [HRLF]; 8 reaches/min), and (2) a high force task (60% of maximum grip strength) performed at low reach rates (low repetitions, high force [LRHF]) or high reach rates (high repetitions, high force [HRHF]).

Using this model, the authors examined the median nerve for decreased nerve conduction velocity (NCV), a common test used in humans to identify nerve injury. By

Table 22-3
Animal Models of Overuse Injuries and Chronic Nerve Constriction Injury in which Peripheral Nerve Tissues Were Examined

Authors	Model	Tissue and Functional Changes
Chronic Nerve Constriction Injury Animal Models (CCI)		
Mackinnon et al.[80] Mackinnon and Dellon[95]	Rat model Silastic tubing–induced chronic compression of median nerves for 1 to 12 months	Nerve compression, nerve demyelination and degeneration; hypervascularity Intraneural fibrosis; regenerating unmyelinated fibers; ↓ NCV
Mackinnon et al.[93] Mackinnon and Dellon[94]	Primate model Silastic tubing–induced chronic compression of median nerves for 4 to 12 months	↓ Neural tissue in fascicles, demyelination, and ↓ number of myelinated fibers Intraneural fibrosis
Okamoto et al.[108]	Rat model Sutures loosely placed around sciatic nerve for 3 to 45 days	↑ IL-1β and IL-6 (at 7 days), TNF-α (at 14 days), and IL-10 (progressive ↑ to 45 days) ↑ Thermal hyperalgesia and mechanical allodynia days 7 to 14; recovery by 45 days
Schäfers et al.[96]	Rat model Sutures loosely placed around sciatic nerve for 18 days Intraneural application of TNF Ibuprofen and celecoxib therapy	CCI-induced mechanical allodynia and thermal hyperalgesia, a result attenuated by early ibuprofen and celecoxib treatment Mechanical allodynia induced by TNF alone, a result attenuated by ibuprofen treatment
Wagner and Myers[100]	Rat model Sutures loosely placed around sciatic nerve for 3 to 9 days IL-10 therapy (endoneurial application)	CCI-induced thermal hyperalgesia, macrophage influx, and TNF-α expression attenuated by IL-10 therapy
WMSD Animal Model		
Al-Shatti et al.[307] Barr et al.[112]	Rat model Voluntary LRLF reaching and grasping task 1 reach/30 min, 45 mg force 2 hr/day, 3 days/week for 12 weeks	Transient ↑ TNF-α in week 12 No motor changes
Al-Shatti et al.[71] Barbe et al.[110,111] Barr et al.[112,113] Clark et al.[78]	Rat model Voluntary HRLF reaching and grasping task 1 reach/15 min, 45 mg force 2 hr/day, 3 days/week for 8 to 12 weeks	Bilateral ↑ in macrophages in median nerves Transient ↑ IL-1α, IL-1β, TNF-α, and IL-6 in median nerves in weeks 3 to 5; ↑ IL-10 in nerve and muscles in week 5 ↑ Intraneural fibrosis in weeks 10 to 12 ↓ NCV of median nerve ↓ Reach rate and task duration; maladaptive movement patterns (raking) began in week 4, bilateral paw withdrawal response threshold to tactile stimulation, ↓ bilateral grip strength
Clark et al.[91]	Rat model Voluntary HRHF reaching and grasping task 1 reach/15 min, 180 g force, 2 hr/day, 3 days/week for 12 weeks	Bilateral ↑ in macrophages in median nerves ↑ Intraneural fibrosis in weeks 10 to 12 ↓ NCV of median nerve > HRLF ↓ Reach rate and task duration > HRLF Maladaptive movement patterns began in week 4 Hypersensitivity initially, then loss of sensation

HRLF, High repetition, low force; *HRHF*, high repetition, high force; *IL-1*, interleukin-1, a proinflammatory cytokine; *IL-6*, both a proinflammatory and an anti-inflammatory cytokine; *IL-10*, anti-inflammatory cytokine; *LRLF*, low repetition, low force; *NCV*, nerve conduction velocity; *TNF-α*, tumor necrosis factor α; *WMSD*, work-related musculoskeletal disorder.

10 weeks a small but significant decrease (9%) was seen in the NCV,[78] which showed that nerve injury accumulates with continued task performance and leads to a clinically relevant loss of function. The decrease in the NCV was even greater (16%) in rats that performed the HRHF task for 12 weeks, which indicates a positive dose-response relationship between the task exposure level and loss of nerve function.[91] Additional findings were a marked increase in macrophages recruited into the median nerve at the level of the wrist, myelin degradation, and epineural fibrosis after the performance of either the HRLF or the HRHF tasks for 9 to 12 weeks.[78,91] The timing of the fibrosis was associated with the reduction in the conduction velocity of that nerve.[78,91] Finally, significant but transient increases were observed in several cytokines (IL-1α, IL-1β, TNF-α, and IL-6) in the median nerve at the level of the wrist and forearm.[71] The decline in production of these proinflammatory cytokines matched temporally with increased production of an anti-inflammatory cytokine, IL-10, which is known to downmodulate the production of proinflammatory cytokines. These findings and others are summarized in Table 22-3.

Central Nervous System Neuroplasticity Associated with Chronic Pain and Inflammation

Neuroplasticity is a persistent anatomical change that occurs in a neuron as a result of repeated activity across a synapse. It occurs during development, regeneration, or in the mature system. Neuroplasticity can occur at any level of the peripheral and central nervous system, including the spinal cord.

Several mechanisms are possible for neuroplasticity, and two are shown in Figure 22-4. The different mechanisms increase the efficacy of a synapse, unmask or enhance previously ineffective sites, produce changes in neuronal morphology, prune unused neuronal processes, or create electrophysiological changes in the neuron. Peripheral nerve injury results in an increased release of excitatory neurotransmitters and neuropeptides (e.g., SP, glutamate, and CGRP) both peripherally from nociceptor terminals and centrally in a dorsal spinal nerve root or in the dorsal nucleus at the level of the medulla.[115-117] The central release activates postsynaptic receptors for these neurotransmitters, which trigger the release of protein kinases or nitric oxide (NO), or both (see Figure 22-4). The molecules then activate intracellular cascades in the postsynaptic neuron. Chronic or repetitive activation of these cascades results in the upregulation of genes, leading to increased production of neuropeptides, hormones, and enzymes, as well as additional receptors. If additional receptors for neurotransmitters/neuropeptides are inserted into the postsynaptic cell membrane, the postsynaptic neuron's ability to bind these molecules is enhanced, which creates a hyperexcitable neuron. Also, as shown in Figure 22-4, NO is a retrograde messenger that can cross cell membranes to the presynaptic cell. It can increase the release of neurotransmitters from the presynaptic neuron, which can also lead to hyperexcitability of this synapse.

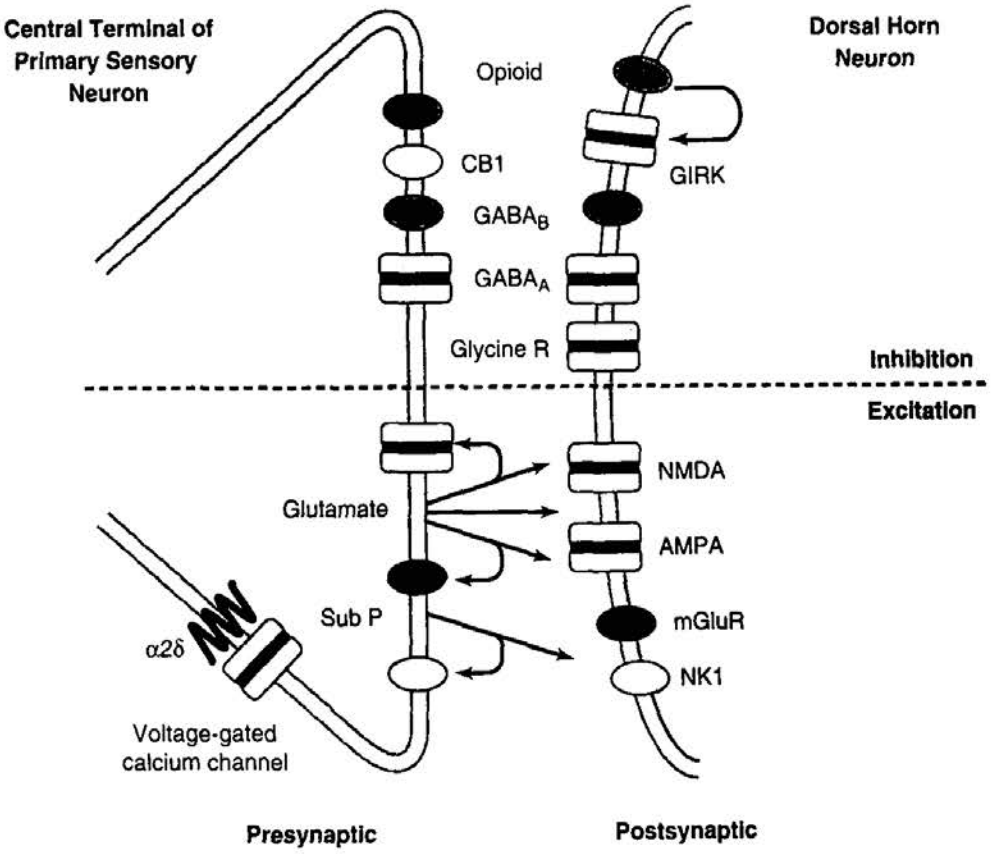


Figure 22-4
Transmission between primary sensory and dorsal horn neurons is subject to presynaptic and postsynaptic excitatory and inhibitory influences. (From Siegel GJ, Albers RW, Brady ST, Price DL: *Basic neurochemistry: molecular, cellular and medical aspects*, ed 7, p 932, Amsterdam, 2006, Elsevier.)

This hyperexcitability may augment the excitability of the dorsal column–medial lemniscus pathway, or it may lead to abnormal sensations in the peripheral nerve, such as hyperalgesia and mechanical allodynia. Woolf and Salter[118] postulated that these clinical symptoms are due to excessive activation of nociceptors (discussed previously). Chronic pain from chronic peripheral inflammation or the application of irritants to the skin leads to similar central changes. Chronic pain appears to change the efficacy of a synapse by increasing the release of neuromodulators or neurotransmitters from nociceptor terminals or by increasing the number of synaptic vesicles in the nociceptor terminal. Chronic pain also has been shown to alter the enzymatic degradation or reuptake of the neurotransmitter or increase the insertion of receptors into the postsynaptic membrane. Nociceptor hyperexcitability, therefore, may play a role in the pathogenesis of abnormal sensations after peripheral nerve injury. The clinical significance of such neuroplasticity is hyperalgesia, hypersensitivity, and sensory dysfunction.

Abnormal Pain Characteristics

- *Allodynia:* Pain is induced by a normally non-noxious stimulus
- *Hyperalgesia:* A painful stimulus evokes pain of a greater than normal intensity
- *Chronic pain:* Pain of long duration; decreased nociceptor threshold (hyperalgesia)

Hypersensitivity and Spinal Cord Neuroplasticity Associated with Repetitive Tasks

The previously discussed studies prompted the authors to use their model to test sensory function. This was done by observing paw withdrawal in response to palmar stimulation using graded Von Frey monofilaments in the HRHF group. Von Frey monofilaments are calibrated fibers used to test mechanical sensitivity with the application of stimulation to the plantar aspect of the paws. A positive response is defined as immediate withdrawal of the paw from the stimulus and frequently includes licking or shaking of the paw. The authors observed an increase in the paw withdrawal threshold at 12 weeks in the HRHF group,[91] a change indicative of a decrease in sensation (hyposensitivity) (Figure 22-5). The loss of sensation most likely was caused by fibrotic compression of the median nerve and injury or compression-induced demyelination of the neural axons. Interestingly, the hyposensitivity was preceded by a decrease in the withdrawal threshold at 2 to 3 weeks, a change indicative of allodynia or hypersensitivity (see Figure 22-5). Although this decrease was not statistically significant in the eight animals tested, it is noteworthy because of its timing with respect to the onset of the inflammatory response.

The authors also examined the spinal cord for changes in response to peripheral inflammation induced by each of the four task groups. Cervical spinal cord segments were examined using antibodies against SP and two of its receptors, neurokinin-1 (NK-1) and N-methyl-D-aspartase receptor-1 (NMDAr1). An increase was seen in the amount of SP present in the laminae II of the dorsal horns of cervical spinal cord segments, as well as SP receptors, between 4 and 8 weeks of task performance; this increase peaked by 6 weeks in the ipsilateral dorsal horn of cervical cords in the HRLF and the HRHF groups.[109]

Peripheral neuroplasticity also has been observed in conjunction with overuse injuries. Increased innervation and increased levels of neurochemicals (e.g., SP, glutamate, and NMDAr1) have also been observed in tendon attached to the lateral epicondyle of the humerus in patients with chronic tendinopathies, such as chronic

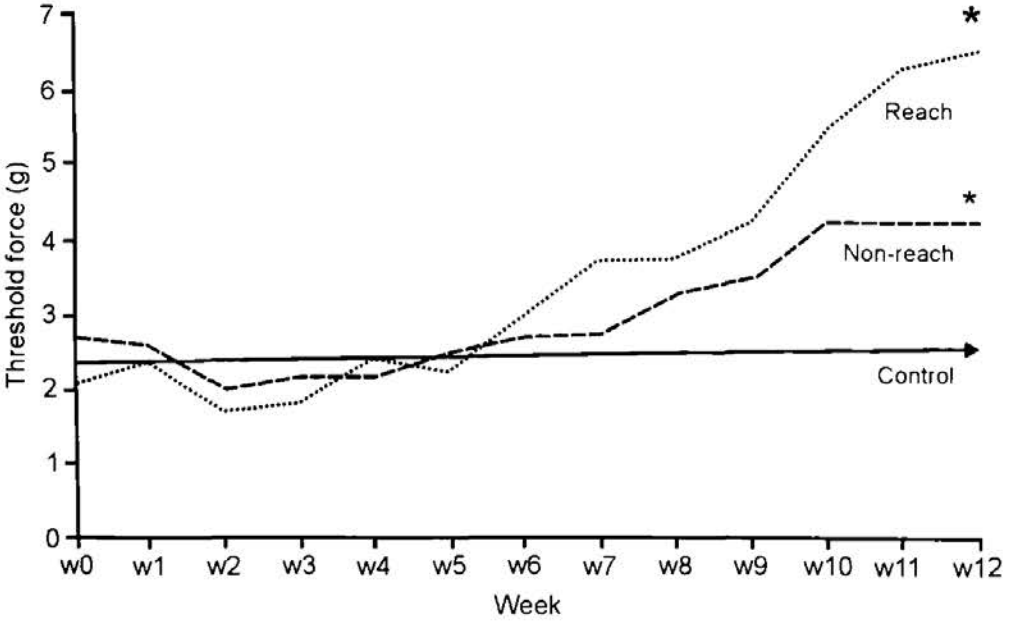


Figure 22-5
Sensory Von Frey outcomes of performing a high repetition, high force (HRHF) task for 12 weeks. Sensory outcomes from the limbs of controls, aged 3 months (n = 15) to 1 year (n = 6), and limbs from experimental rats (reach and nonreach limbs) are depicted (n = 8). The threshold force needed to stimulate a withdrawal of the limb increased dramatically over weeks of task regimen. The sensory threshold of the 1-year old control rats *(arrow)* did not decline from that of the 3-month-old control rats. Σ:p <0.01.

tennis elbow.[119-123] Using the rat model, the authors found increased levels of SP in flexor forelimb tendons by 3 weeks in the HRHF rats, with additional increases by 12 weeks.[125]

Although, direct correlations need to be made, these human and animal findings suggest that increased neuronal innervation, as well as increased release of neurochemicals from activated nociceptor terminals into peripheral tendon tissues, is linked to painful tendinopathies. Therefore central or peripheral neuroplasticity (or both) may be an underlying cause of some of the motor changes observed in patients with painful tendinopathies.

Evidence of Musculotendinous Injury and Inflammation in the Development of Overuse Injuries

Musculotendinous injuries caused by repetitive and/or forceful tasks are due to repeated overstretching, compression, friction, and ischemia.[90,92,126-128] These insults lead to mechanical injury of membranes and intracellular structures.[81,127,128] The authors hypothesize that these injuries first lead to acute inflammatory responses. If injury and acute inflammation occur repeatedly (as might be the case with a moderate to high demand repetitive task in which the injury cycle overshoots healing), then chronic inflammation, fibrosis, and perhaps even tissue breakdown (disorganization and degeneration) result.

Human Findings

Human studies examining tendons and tendosynovial biopsies from patients with chronic tendinopathies (e.g., epicondylitis, epicondylalgia, tendinosis, and CTS) have found evidence of increased levels of neurochemicals, angiogenesis, inflammatory mediators, fiber and matrix disorganization, and fibrosis (Table 22-4).[86-89,119,121,122,127-130] It should be noted that not all the studies in Table 22-4 found each of these tissue changes. Because only a limited amount of tissue can be collected during a biopsy, the number of questions that can be pursued is limited in a human study. Even so, these studies show that repetitive tasks often lead to fibrotic and degenerative tendon changes and that these changes often are accompanied by localized increases in neurochemicals and their receptors, as well as pain. Furthermore, a study by Hirata et al.[89] showed that the levels of metalloproteinases (MMPs), which are enzymes involved in collagen degradation, correlated with pain severity and that tendon synovial fibrosis increased over time in these patients.

Studies also have been performed on muscle tissue biopsied from patients with long-term chronic overuse syndromes (see Table 22-4). These studies showed evidence of muscle tissue changes, including myopathic changes such as inflammation, muscle fiber necrosis, and cell metabolic changes consistent with injury, denervation, and/or ischemic loss of muscle fibers.[124,131-134]

Serum markers of injury also have been found in patients with overuse injuries. Freeland et al.[129] detected increased serum malondialdehyde, an indicator of cell stress, in patients with CTS. Kuiper et al.[135] found higher levels of biomarkers of collagen degradation and synthesis in a group of student nurses with high numbers of patient handling tasks. Recently, Kuiper et al.[136] examined serum for biomarkers of collagen synthesis and degradation in construction workers involved in heavy manual materials handling. The serum results were compared to those from sedentary workers. Although the levels of collagen synthesis and degradation products were both increased in the workers involved in heavy manual tasks, the overall ratio of the synthesis product to degradation product remained the same as in the sedentary control workers. These results suggested that the tissues had undergone adaptive responses that protected them from unresolved degradation.

A recent pilot study by Carp et al.[137] detected proinflammatory cytokines in the serum of patients treated in an outpatient physical therapy clinic for diagnoses related to severe overuse injuries. The patients were classified into three groups according to symptom severity, as measured by the Upper Body Musculoskeletal Assessment tool (UBMA):[138] mild (UBMA score 51-75; n = 9), moderate (UBMA score 76-100; n = 9), and severe (UBMA score >100; n = 9). A control group was used for comparison; it consisted of unaffected individuals with a UBMA score below 50 (n = 9). The serum results showed significant increases in all proinflammatory cytokines in patients with severe overuse injuries, as well as increases in IL-6 in patients with moderate and mild overuse injuries.[138] Because inclusion in this pilot study required a duration of symptoms no longer than 12 weeks, these findings support the presence of an early inflammatory process in the development of overuse injuries.

One of the challenges involved in studying workers is the difficulty determining the causality between tissue and behavioral responses. Presumably, the initiating injury stimulus is long since past, and the condition of the tissues has been substantially altered from the preinjury state. Whether task-induced injury is followed by inflammation is a point of controversy in the literature, because tissues removed from patients at the time of surgery are collected long after the inflammatory response has resolved. Therefore it is impossible to conclude whether biochemical changes, for example, cause or follow the physiological mechanisms that led to the patient's current clinical presentation.

Animal Studies

A number of animal studies have related exercise loading of tendons to early inflammatory changes (Table 22-5). A study by Nakama et al.[139] found evidence of tendon injury after cyclical loading of the flexor digitorum profundus muscle for 13 weeks at a repetition rate of 2 hours per day, 3 days per week. They observed microscopic

Table 22-4
Selection of Human Studies of Overuse Injuries in which Serum or Musculotendinous Tissues Were Examined

Authors	Description of Patients	Tissue and Functional Changes
Tendon and Tendosynovial Biopsies		
Alfredson et al.[120-122]	ECRB tendon microdialysis, ultrasonography, Doppler, and biopsies of patients with chronic lateral epicondylitis or chronic Achilles tendinosis	↑ Glutamate (mediates pain); ↑ NMDAr1 PGE_2 not upregulated in tendon Irregular fiber structure, focal hypoechoic areas Angiogenesis and ↑ innervation of these vessels
Åstrom et al.[130]	Achilles tendon biopsies from 27 patients with chronic Achilles tendonitis	Slight inflammation, bursitis, or fibrosis in five patients Fiber disorganization and activated tenocytes
Campligio et al.[86]	Flexor tendosynovial biopsies from 50 patients with idiopathic CTS	Disorganization and degeneration of collagen fibers Diffuse fibrosis of tendon sheath ↑ Vascularity and arteriosclerosis
Ettema et al.[87]	Subsynovial connective tissue (loose areolar tissue deep to flexor tendons) biopsies from 30 patients with CTS	↑ Fibroblasts, collagen fiber size, and vascular proliferation ↑ Collagen type III fibers; ↑ fibroblasts expressing TGF-β RI
Fenwick et al.[74]	Achilles tendon biopsies from 7 patients with chronic Achilles tendinopathy	Hypercellular, hypervascular; ↑ TGF-β/TGF-β RII Disorganized tendon matrix; ↑ glycosaminoglycan
Freeland et al.[129]	Flexor tendosynovial biopsies and serum examined in 41 patients with CTS	↑ Malondialdehyde in serum and flexor tendosynovium ↑ PGE_2 and ↑ IL-6 in flexor tendosynovium (not in serum)
Hirata et al.[88,89]	Flexor tendosynovial biopsies and pain severity testing in 40 patients with CTS; patients divided into symptom duration groups (less than 4 months to longer than 12 months)	Proliferative arteriosclerosis; correlates with symptom duration ↑ MMP-2; correlates with pain severity ↑ Synovial fibrosis with disease progression ↑ PGE_2 and VEGF at 4-7 months of symptom duration
Ljung et al.[123]	Flexor tendon biopsies from five patients with tennis elbow (lateral epicondylitis); four patients with medial epicondylalgia	SP and CGRP immunoreactivity in all tendons NK1-R immunoreactivity also in lateral epicondyle tendons

Muscle Biopsies		
Kadi et al.[131,308]	Trapezius biopsies from 21 female and 10 male workers with trapezius myalgia, nine male workers without myalgia, and six male controls	Females: ↑ Area and proportion of type I fibers; ↓ capillary: area type I fiber ratio in patients with high pain scores Males: ↑ Frequency of type II fibers, vascularity, developmental myosin in myalgia group; mitochondrial organization and COX-negative fibers in myalgia group and occupational controls
Larsson et al.[309]	Trapezius biopsies from 17 female workers with trapezius myalgia; Doppler testing of trapezius blood flow	Moth-eaten and ragged red type I muscle fibers worse on pain side; atrophic muscle fibers and fiber splitting ↓ Blood flow; correlates with pain and ragged red fibers
Larsson et al.[133,134]	Trapezius biopsies from 25 female workers with trapezius myalgia (CM); 25 workers without trapezius myalgia (CC); 21 healthy controls (TC)	↓ Capillary: muscle fiber area in CM; moth-eaten muscle fibers in CM and CC (4%) greater than in TC (2%) Prevalence of ragged red fibers related to working activities and having tender point in trapezius muscle
Ljung et al.[124]	ECRB muscle biopsies from 26 patients with lateral epicondylitis longer than 7 months	Abnormal muscle NADH staining; muscle necrosis No evidence of muscle inflammation ↑ Type IIA fibers and muscle fiber regeneration
Serum Samples		
Carp et al.[138]	Serum collected from 27 patients diagnosed related to work-related MSDs, nine controls; patients divided into groups based on severity of symptoms	↑ IL-6 in mild and moderate WMSD groups ↑ IL-6, IL-1α, and TNF-α in severe WMSD group
Kuiper et al.[135]	Serum collected from student nurses with patient-handling activity for 6 months	Higher biomarkers of type I collagen anabolism in exposed group; ↑ with higher exposure levels
Kuiper et al.[136]	Serum collected from male construction workers performing heavy manual materials handling tasks	↑ Type I collagen and ↑ collagen synthesis; no difference in ratio of collagen synthesis to degradation compared to sedentary control workers

CGRP, Calcitonin gene-related peptide; *COX*, cyclo-oxygenase; *CTS*, carpal tunnel syndrome; *ECRB*, extensor carpi radialis brevis; *IL-1*, interleukin 1, a proinflammatory cytokine; *IL-6*, interleukin-6, both a proinflammatory and an anti-inflammatory cytokine; *MMP-2*, matrix metalloproteinase, a collagenase; *MSDs*, musculoskeletal disorders; *NADH*, nicotine-adenine-dinucleotide reductase; *NK-1*, Neurokinin 1, a substance P receptor; *NMDAr1*, *N*-methyl-D-aspartase receptor-1 a glutamate receptor; PGE_2, prostaglandin E_2; *SP*, substance P; *TGF-β*, transforming growth factor *β*; *TNF-α*, tumor necrosis factor *α*, a proinflammatory cytokine; *VEGF*, vascular endothelial growth factor.

Table 22-5
Animal Models of Overuse Injuries in which Serum or Musculotendinous Tissues Were Examined

Authors	Model	Tissue and Functional Changes
Studies Examining Tendons		
Archambault et al.[141]	Rabbit model of Achilles tendinosis Controlled kicking 20 and 75 rep/min, 1 to 2 hr/day, 3 days/week for 6 to 8 weeks	Hypercellularity and ↑ inflammatory cells in tendons; ↑ TNF-α, IL-1 ↑ mRNA of matrix components (e.g., ↑ collagen)
Archambault et al.[142]	Rabbit model of Achilles tendinosis Controlled kicking 75 rep/min, loading of 1.2 Hz, 20 N 2 hr/day, 3 days/week for 11 weeks	No evidence of inflammation ↑ mRNA expression of collagen type III and MMPs
Backman et al.[140]	Rabbit model of Achilles tendinosis Controlled kicking 150 rep/min, 2 hr/session 3 days/week for 5 to 6 weeks	Tendon necrosis, tendon matrix reorganization ↑ Vascularity, ↑ inflammatory cells and edema in paratendon Paratendon fibrosis
Carpenter et al.[143] Soslowsky et al.[144]	Rat model Treadmill running loading of supraspinatus tendon with and without external compression via Achilles tendon allograft 17 m/min on a decline 1 hr/day, 5 sessions/week, up to 16 weeks	Hypercellularity, ↑ tendon cross sectional area Collagen disorganization, rounded tenocytes ↓ Maximum biomechanical stress Tissue changes ↑ with exposure (compression or time)
Messner et al.[145]	Rat model Eccentric loading of Achilles tendon 30 cycles/min 1 hr/day, 3 sessions/week for 7 to 11 weeks	Fibrillation of epitendon ↑ Vascularity of epitendon; ↑ SP and CGRP in epitendon and paratendon Limping gait
Nakama et al.[139]	Rabbit model of medial epicondylitis Cyclical loading of flexor digitorum profundus muscles; tendon examined; 2 hr/day, 3 days/week, for 80 hours total	↑ Microtear area, ↑ tear densities, and ↑ tear size at medial epicondyle attachment site in loaded limbs Regional differences: Outer enthesis > inner enthesis
Topp and Byl[254]	Primate model Repetitive, forceful hand squeezing in owl monkeys 15 squeezes/min, 300 trials/day for 2 to 5 months	Tendon hypercellularity and disorganized collagen in digital flexor tendons of one of three monkeys, attributed to anatomical anomaly No signs of active inflammation in hand tendons
Studies Examining Muscles		
Stauber et al.[127,128]	Rat model Forced lengthening of soleus muscle Slow (10 mm/sec) or fast (25 mm/sec) strain rates 3 sessions/week for 4 to 6 weeks	Hypertrophy, ↑ muscle mass, ↑ myofiber area (adaptation) after slow stretch; ↑ muscle mass, ↓ myofiber area after fast stretch Splitting of myofibers and ↑ type A fibers (regeneration) after fast stretch; collagen struts after slow stretch; clear fibrosis after fast stretch
Stauber et al.[81]	Rat model Forced lengthening (eccentric contractions) of soleus muscle 50 strains/day, 5 sessions/week for 6 weeks Followed by 3 months of cessation of chronic hyperactivity	Hypervascularity ↓ Muscle mass, ↓ myofibers area ↑ Noncontractile tissue, ↑ collagen content Incomplete recovery of tissue changes after 3 months
Studies Examining Muscles, Tendons, and/or Serum		
Barr et al.[112] Fedorczyk et al.[125]	Rat model Voluntary LRLF reaching and grasping task 1 reach/30 min, 45 mg force 2 hr/day, 3 days/week for 12 weeks	No ↑ SP, NMDAr1, or CGRP in epitendon, paratendon, or forelimb muscles No increase in serum IL-1α (only serum examined)

Table 22-5
Animal Models of Overuse Injuries in which Serum or Musculotendinous Tissues Were Examined—Cont'd

Authors	Model	Tissue and Functional Changes
Barbe et al.[111] Barr et al.[112,113] Barr and Barbe[84]	Rat model Voluntary HRLF reaching and grasping task 1 reach/15 min, 45 mg force 2 hr/day, 3 days/week for 8 to 12 weeks	Forearm flexor tendon microfraying Widespread ↑ in macrophages in all muscles, tendons and CTs examined in weeks 3 to 6; ↑COX-2 and IL-1β in cells of muscles, tendons Paratendon fibrosis in weeks 8 to 12 ↑ hsp72 in distal forelimb and palm by week 3 ↑ Serum IL-1α
Fedorczyk et al.[125]	Rat model Voluntary HRHF reaching and grasping task 1 reach/15 min, 180 g force, 2 hr/day, 3 days/week for 12 weeks	↑ SP, NMDAr1, and CGRP in epitendon and paratendon of forelimb muscles
Jarvinen et al.[310]	Rat model Casting for 3 weeks followed by progressively increasing low and high intensity treadmill running, 5 days/week for 7 weeks	Recovery of ↑ tenascin C in myotendinous junction and tendon in dose-dependent manner with treadmill running after casting No de novo synthesis of tenascin C in muscle

CGRP, Calcitonin gene-related peptide; *COX-2*, cyclo-oxygenase 2; *CT*, loose areolar and synovial connective tissue; *IL-1*, interleukin-1; *HRLF*, high repetition, low force; *HRHF*, high repetition, high force; *hsp72*, inducible form of heat shock protein 70/72; *LRLF*, low repetition, low force; *MMPs*, matrix metalloproteinases; *mRNA*, messenger ribonucleic acid; *NMDAr1*, *N*-methyl-D-aspartase receptor-1, a glutamate receptor; *Rep*, repetitions; *TNF*, tumor necrosis factor; *SP*, substance P.

microtears in the tendons at their epicondylar attachment to the humerus. Backman et al.[140] reported on the use of a controlled kicking model in the rabbit that induced Achilles tendonitis. Inflammatory processes, such as increased vascularity and increased inflammatory cells, were observed in the paratenon, and evidence of necrosis, reorganization, and fibrosis were observed in the tendon by 5 weeks of repetitive kicking.

Archambault et al.[141,142] also found evidence of an inflammatory response and fibrotic responses in the paratenon using this model. They observed increases in proinflammatory cytokines (IL-1 and TNF-α) and increased messenger ribonucleic acid (mRNA) levels of matrix molecules (e.g., collagen type I) by 6 to 8 weeks of task performance. When the kicking protocol was prolonged to 11 weeks, the inflammatory response apparently resolved and remodeling responses occurred (e.g., increased mRNA for collagen type III) in the tendon and paratenon.

Carpenter et al.[143] and Soslowsky et al.[144] developed a rat model of running-induced rotator cuff tendinopathy. Similar to the studies by Backman et al. and Archambault et al., they found evidence of inflammation and fibrosis (hypercellularity and tendon thickening) after 4 weeks of running. These tissue changes persisted through 16 weeks. They also found that biomechanical tissue tolerance decreased in the tendons of experimental animals compared to controls.

Chronic, repetitive contraction of muscles often leads to maladaptive fibrotic repair. Studies by Stauber et al.,[127,128] using a rat model of muscle force-lengthening (eccentric contraction), indicated that repeated muscle strains at fast velocities result in myopathic changes, including muscle fiber splitting, infiltration of macrophages, and fibrosis. These changes are in direct contrast to the compensatory, adaptive responses that occur with repeated slow strains of muscles. Increasing the exposure and duration of repeated forced-lengthening leads to significant decreases in muscle mass and myofiber area and increases in noncontractile tissues (see Table 22-5). In another study, Stauber et al.[81] found that recovery from pathophysiological fibrotic changes is slow, even with complete cessation of the repeated strains for 3 months; this highlights the importance of prevention in the management of such disorders.

In the authors' model of upper extremity overuse injuries in the rat, evidence of musculotendinous damage was found in the forearm flexors of the reach limbs of the rats training under a high rate of repetition with low force (HRLF).[111] Immunohistochemical analyses showed that this tendon disruption was accompanied by an increase in activated exudate macrophages by 6 weeks of task performance. Increases in macrophages in loose connective tissues and at sites of muscle and ligament attachments to bone also were found in these HRLF animals. The increase in the numbers of macrophages rose significantly above those of control animals as early as 3 weeks and peaked at 5 to 6 weeks. Serum levels of IL-1α in these animals increased significantly above control levels in week 8.[111,112] IL-1α did not change significantly with task performance in a low repetition, negligible force (LRNF) group (2 to 4 reaches/min at 15% of maximum grip

strength).[112] The authors hypothesized that the net cytokine production in the LRNF group allowed for maintenance of homeostasis through the resolution of an acute inflammatory response. The level of repeated incidents of mechanical injury to the tissues in the HRNF group, on the other hand, led to a net production of IL-1α, indicative of a chronic and systemic inflammatory response to the repetitive task.

Behavioral Changes That Coincide with Tissue Inflammation in Severe Overuse Injuries

The authors have reported on behavioral indicators in the rat model that offer insight into the behavioral consequences of injury and inflammation. The reach rate (RR; reaches/min) is an indicator of the animals' ability to maintain task pace. The reach movement pattern is an indicator of the quality of reaching. The HRLF group showed a significant decline in RR in week 6, which coincided with the peak inflammatory response, and a return toward baseline in week 8.[111,113] The LRLF group did not exhibit any change in RR over 12 weeks.[112] However, the HRHF group underwent a significant decline in RR in weeks 3 to 6 and a significant decrease in sensation, grip strength, and NCV in week 12.[91] All HRLF animals developed progressively degraded reach movement patterns by 7 weeks of task performance, whereas only 60% to 70% of LRLF animals showed reach movement pattern degradation.[111,112]

Messner et al.[145] reported behavioral changes that develop in their rat model of eccentric loading of the Achilles tendon. Using a repetitive task of 30 cycles/min for 1 hour per day, 3 days per week, for 7 to 11 weeks total, they observed the development of a permanent limping gait that was associated with fibrillation of the epitendon (the outer sheath of the tendon), as well as angiogenic changes and increased expression of neurochemicals in this same tendon region.

These behavioral changes are summarized in Table 22-5, along with the tissue changes observed in the particular study. The findings indicate that functional declines may accompany tissue injury and inflammation. Figure 22-6 shows a timeline that postulates the onset of behavioral changes in relation to the pathological tissue responses.

Role of Proinflammatory Cytokines in "Sickness Behavior"

The psychoneuroimmunological effects of proinflammatory cytokines, specifically IL-1β, TNF-α, and IL-6, have been studied extensively in animal models over the past decade

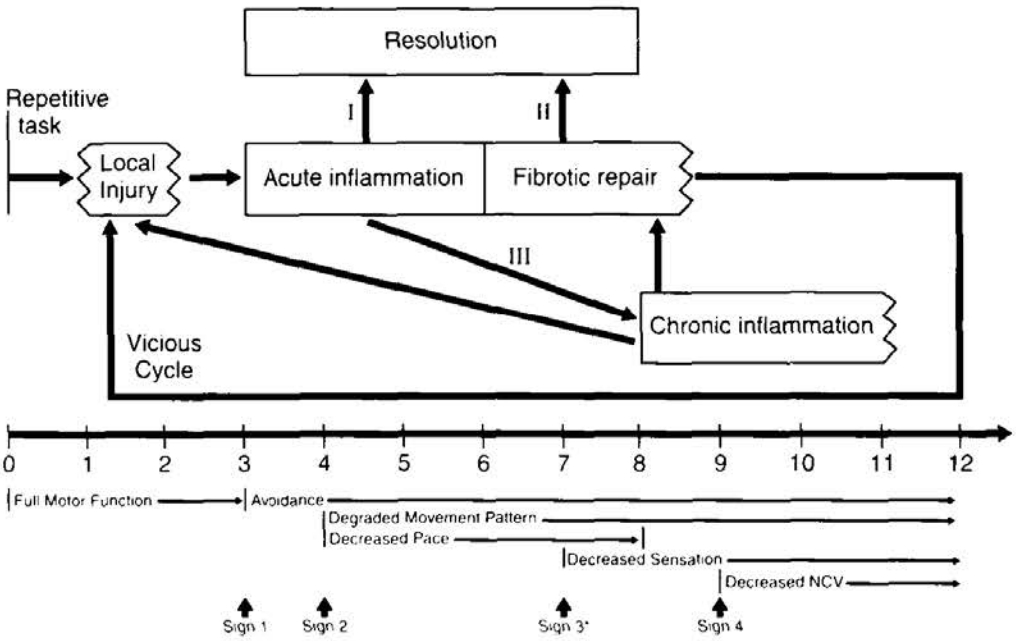


Figure 22-6

Steps in the inflammation mediated development of work related musculoskeletal disorders. The vertical zigzagged boundaries indicate uncertainty as to the specific time frame for transitions between progressive steps. The timeline at the bottom of the figure relates these inflammatory events to observations of behavioral indicators in a rat model. At the very bottom of the figure, the physical sign (behavior degradation) that reflects underlying pathophysiology is indicated. The three possible exposure-dependent outcomes in this schematic are indicated as follows: (1) acute inflammation followed by resolution and restoration of normal tissue, as in the LRLF group; (2) acute inflammation followed by fibrotic repair, as in the HRLF group; and (3) acute inflammation followed by chronic systemic inflammation, with or without fibrotic repair, and initiation of a vicious cycle of further injury and inflammation, as in the HRHF group. *LRLF*, Low, repetition, low force; *HRLF*, High repetition, low force; *HRHF*, High repetition, high force. (Modified from Barr AE, Barbe MF: Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders, *J Electromyogr Kinesiol* 14:82, 2004.)

for their contribution to a constellation of physiological and behavioral responses known collectively as the *sickness response*. These responses include fever, weakness, listlessness, hyperalgesia, allodynia, decreased social interaction and exploration, somnolence, decreased sexual activity, and decreased food and water intake.[146-149] The sickness response is adaptive in that it results in behavior that minimizes energy expenditure in order to allocate metabolic resources to fighting infection or disease.[146] Furthermore, a sickness response has been shown to be a motivational state with respect to feeding behavior in animals.

"Sickness Responses" Mediated by Proinflammatory Cytokines

- Fever
- Weakness
- Decreased social interaction/exploration
- Somnolence/listlessness/lethargy
- Decreased food and water intake
- Decreased sexual activity
- Hyperalgesia/allodynia

Aubert et al.[150] demonstrated that rats injected with IL-1β reduced the frequency of lever presses to receive a food reward but readily ate food when it was freely presented to them. The interpretation of these results from the motivational standpoint suggests that IL-1β produces an aversion to foraging, which is an energy-intensive activity, rather than to feeding per se. In the authors' model, animals exhibited dose-dependent task avoidance over weeks of task performance.[78,91] The HRLF group declined in duration in week 3, then regained baseline duration by week 6.[78] This avoidance of the task in week 3 matches the onset of inflammatory cytokine production in the median nerves in our model,[71] and the recovery to baseline duration matches temporally the increased production of an anti-inflammatory cytokine, IL-10. The mechanism of action of the proinflammatory cytokines on such behavioral responses has been partly elucidated but is still a subject of intense research. The role of the vagus nerve in facilitating a paracrine signal transduction pathway to the hypothalamic-pituitary-adrenal (HPA) axis has been the most extensively studied in rodent models of bacterial infection.[146] An immediate response to intraperitoneal injection of lipopolysaccharide (LPS), a bacterial endotoxin, is the induction within 60 minutes of IL-1β in the abdominal vagus nerve by glial cells and macrophages.[147] Blocking either the vagus nerve or IL-1β activity reduces sickness behaviors associated with LPS injection. Although these latter findings seem to implicate the vagus nerve in particular, the disease model in this case was most consistent with visceral infection or inflammation. These findings raise the possibility that other peripheral nerves are also capable of facilitating signal transduction between local inflammatory mediators and the HPA axis, inducing a sickness response. Recent studies of bilateral neuropathic pain (i.e., hyperalgesia or allodynia) with a unilateral sciatic nerve lesion strongly suggest that other peripheral nerves are capable of such peripheral-central communication.[151-153]

More recent attention has been given to the possible role of serum circulating proinflammatory cytokines in the etiology of depression and other mood disorders, particularly among cancer patients treated with proinflammatory cytokine therapy.[154] The possibility for patients with chronic inflammatory conditions to succumb to the depressive effects of local and systemic proinflammatory cytokines has implications in the management of severe overuse injuries.

Symptoms of depression and anxiety have been reported in numerous epidemiological and clinical studies of patients with severe overuse injuries.[8,155-157] Bystrom et al[158] reported a lower pressure-pain threshold among women automobile assembly line workers with newly reported work-related forearm and hand symptoms. All of these findings in workers with work-related symptoms may be attributed to the sickness response, which suggests a physiological basis for such symptoms. A more complete understanding of the relationship between repetitive and forceful task demands and induction of the sickness response will help direct effective workplace and clinical management strategies that can reduce the stigmatization often imposed by health care providers on patients who present with such vague and apparently psychological complaints.

Summary

By examining the findings of human and animal studies done on severe overuse injuries, the authors have developed a proposed mechanism of pathophysiological and behavioral changes associated with these injuries.

First, repetitive activity leads to a disruption of cells and tissues (Figure 22-7). This injury activates the acute inflammatory response: infiltration of immune cells into the injury site and increased production of cytokines by these immune cells and by injured cells and tissues. The acute inflammatory response then activates mechanisms of cell proliferation and matrix production related to wound healing. Unfortunately, the continued cycle of tissue trauma by continued performance of the repetitive task halts the process of tissue repair at this point.[84,159] Instead, a chronic inflammatory response (with associated secondary tissue damage) is stimulated, along with an excessive fibrogenic response. This postulated mechanism is supported by the many studies, both human and animal, that have found evidence of tendon tissue thickening and fibrosis, nerve and muscle fibrosis, and tissue disorganization and necrosis. Motor behavior changes related to tissue damage, pain, or both would be clearly apparent at this point as a result of nerve damage, and sensory losses may also be present. Finally, a systemic response is stimulated, apparently by the release of cytokines into the bloodstream from the

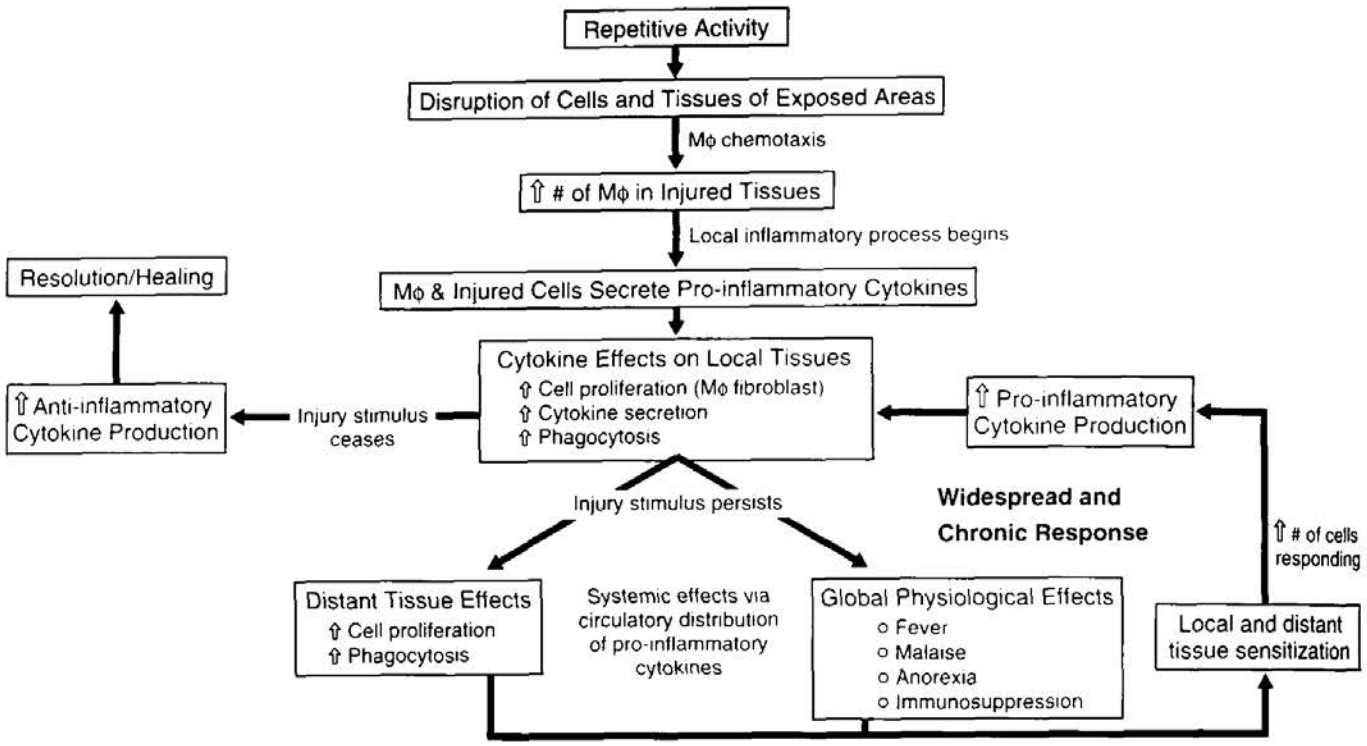


Figure 22-7
Proposed mechanism for the role of systemic distribution of cytokines in widespread symptoms of work-related musculoskeletal disorders. A unilateral, repetitive activity induces a localized inflammatory response. If the injury stimulus ceases, the acute inflammatory response resolves and healing occurs. If the injury stimulus persists, circulating cytokines affect tissues not directly involved in task performance (e.g., inducing inflammation, resorption, degeneration, and malaise depending on the level of cytokines and the tissue type), or they have global physiological effects. Initiation of the systemic response sensitizes tissues, both local and distant from the injury stimulus, and causes further upregulation of proinflammatory mediators. Hence the cycle of widespread and chronic effects is propagated. ⇧, Increase; *Mϕ*, macrophage. (Modified from Barr AE, Barbe MF, Clark BD: Systemic inflammatory mediators contribute to widespread effects in work-related musculoskeletal disorders, *Exerc Sports Sci Rev* 32:141, 2004.)

injured tissues and immune cells still present in the tissues. As shown in Figure 22-7, circulating cytokines can stimulate several global responses, including widespread stimulation of macrophages and cell proliferation, local and distant tissue sensitization, and sickness behavior. The presence of chronic pain and other symptoms of central neuroplasticity stimulate a variety of sensorimotor behavioral consequences (discussed in detail in the next section).

Central Consequences and Treatment Implications of Chronic Repetitive Overuse Injuries of the Upper Limb: Focal Hand Dystonia

The Problem

Stressful, repetitive use of the upper limb in work or sports can lead to acute pain and loss of function. As the first part of the chapter showed, the evidence for microtrauma is convincing. Rest, anti-inflammatory medications, a change in biomechanics, and good ergonomics usually are effective treatment modalities. Unfortunately, some repetitive strain injuries become chronic, and degenerative changes are found in tendons and muscles, scarring restricts soft tissue and joint mobility, compression of peripheral nerves causes strain and limits excursion and, in some cases, involuntary co-contractions of flexors and extensors lead to painless, uncontrollable, end range twisting movements that interfere with the performance of target tasks. This movement dysfunction is referred to as *occupational hand cramps, musician's cramps, keyboarder's cramps, golfer's yip,* and *focal hand dystonia*. Research studies report evidence of degradation of the somatosensory representation of the hand in animals and patients with dystonic hand movements and the need for learning-based training to reorganize the brain.

In this section of the chapter, the authors summarize the principles of neuroplasticity and the origin, diagnosis, and treatment of focal hand dystonia; they also review the research evidence supporting aberrant learning as an approach to the remediation of this condition.

Our hands allow us to perform delicate, complex, individuated, fine motor movements.[160-162] These skillful movements are associated with large, orderly, somatotopic, highly differentiated representations of the hand in the thalamus, basal ganglia, and cortex (Figure 22-8).[163-166] Integrative functional representations of well-learned tasks (e.g., playing an

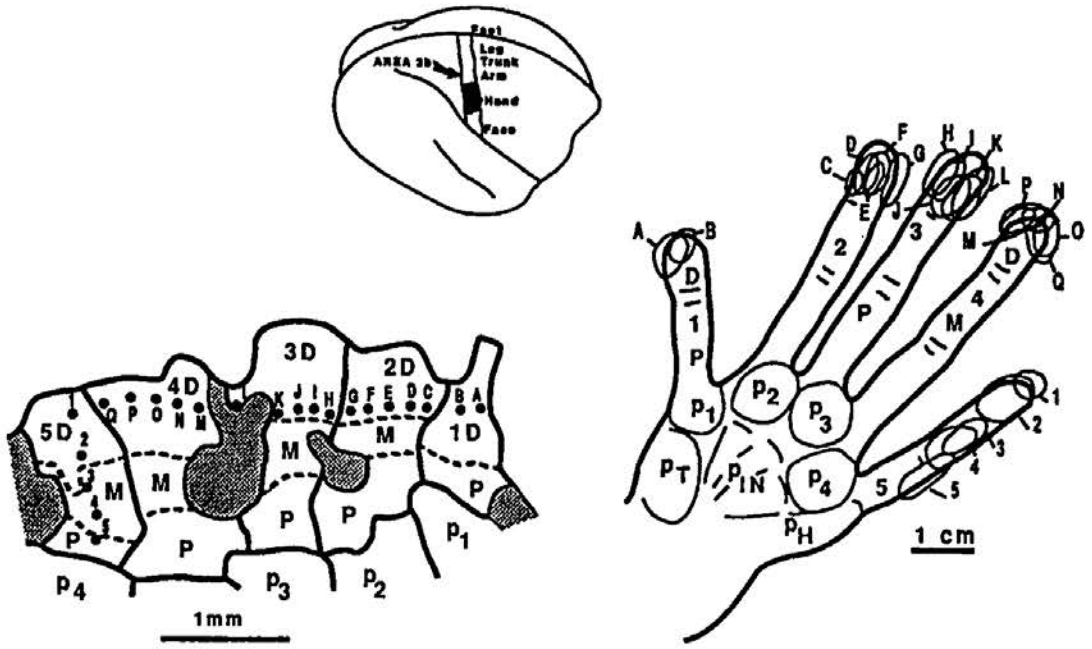


Figure 22-8

Representative normal somatosensory map of the hand with small receptive fields. The digits are organized from distal to proximal. (From Byl NN, Merzenich MM, Cheung S et al: A primate model for studying focal dystonia and repetitive strain injury: effects on the primary somatosensory cortex, *Phys Ther* 77:273, 1997.)

instrument or writing) are also mapped on the cortex.[167] These topographical representations can be modified over a lifetime by attended, repetitive behaviors.[168] Some of these behaviors lead to positive adaptation, and others lead to negative adaptation. For example, situations such as deprivation, drug use, negative feedback, and repetitive, near simultaneous, stereotypical behaviors can degrade the topographical representation of the hand (Figure 22-9), whereas environmental and personal enrichment and attended, rewarded, spaced, repetitive, learning-based, goal-directed, nonstereotypical, progressive practice can lead to positive changes.[166,168-172]

Task practice (mental or physical) enhances the efficiency of learning new tasks, improves task proficiency, and enhances recovery after neural insults.[168,171,173-178] These task-specific, learning-based, repetitive behaviors drive selective changes in cortical cell differentiation and selective specialized representations. New synaptic networks (engrams) are refreshed, and poor connections can be erased as a result of variation in inputs, metabolic state, emotions, sleep, and natural endorphins.[179-181] The physiological changes occur nearly simultaneously with the emergence of more efficient, accurate, and differentiated behaviors;[182-186] upregulation of neurotransmitters such as dopamine and acetylcholine occurs[187,188] as well as changes in neural organization (e.g., expansion of cortical representations, reduction in the size of receptive fields, narrowed columnar spread, co-selection of complementary inputs, increased excitable neurons, enhanced salience and specificity of feedback, increased myelination, strengthened synapses between coincident inputs, shortened integration time, and increased complexity of dendritic branching).[165,173,174,178,189-197]

Unfortunately, neural plasticity is not infinite; inherent limits are based on physiological time constants, inhibition, and integration time.[198] For example, rapid inputs that occur within the inhibitory or integration period may no longer be registered as temporally distinct.[166,199-206] In this case, stimulated skin surfaces form a unified rather than a unique spatial and temporal representation in the cerebral cortex.[173,200] Specificity of digital representation is critical to maintenance of the normal sensory organization, sensorimotor feedback, and fine motor control of the digits.[207,208] Loss of differentiation of somatosensory inputs or blocking of sensory afferents can lead to abnormal motor movements.[209]

Signs of Aberrant Learning

Pain

- Usual signs of redness and swelling are absent
- Pain is out of proportion to use
- Pain is delayed a few hours after activity
- Patient is pain free in most tasks, but pain returns when patient places hands on target instrument

Abnormal Involuntary Movement

- Involuntary movements and tension interfere with target task
- End range posturing restricts purposeful contractions
- Freezing (co-contraction of extensors and flexors) dominates movement
- Tremor-type movements replace smooth movements
- Excessive force replaces graded movements

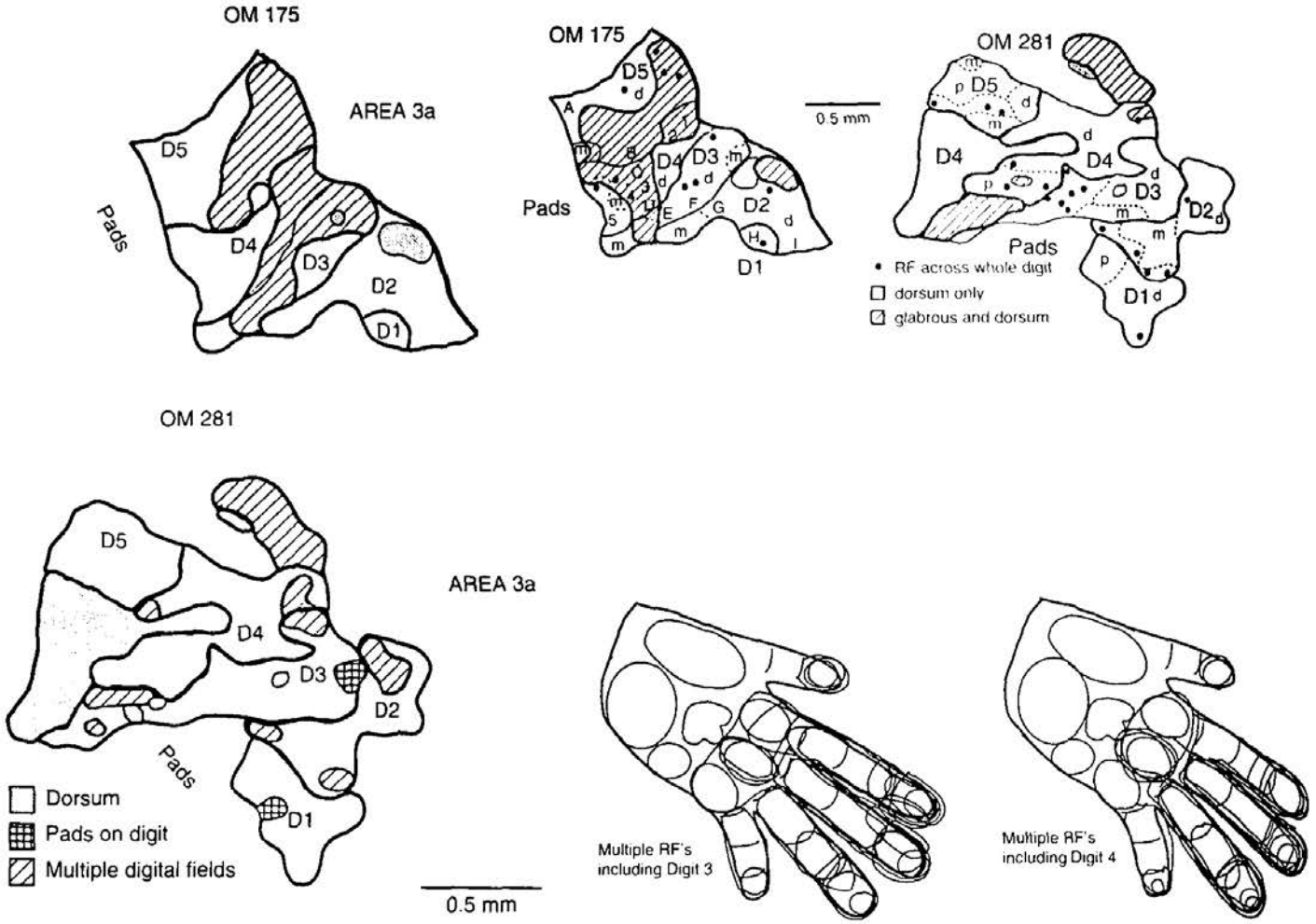


Figure 22-9

Abnormal somatosensory map of the hand after excessive repetitive training. Large receptive fields overlap adjacent digits, adjacent segments, and dorsal and glabrous surfaces. (From Byl NN, Merzenich MM, Cheung S et al: A primate genesis model of focal dystonia and repetitive strain injury. I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys, *Neurology* 47:513-515, 1996.)

Focal Hand Dystonia: A Repetitive Strain Injury Leading to Aberrant Learning?

Etiology

Occupational hand cramps (or focal hand dystonia [FHd]) is considered idiopathic. However, individuals who perform tasks requiring intensive repetitive movements (e.g., working at a computer, playing an instrument, pitching a ball, screwing nails, playing golf) appear to be at high risk. This hand dystonia is described as painless, clumsy hand movements characterized by involuntary, writhing, twisting end range movements that interfere with the performance of specific target tasks.[210-219] It is hypothesized that focal dystonia is genetic,[220-223] although strong evidence of an imbalance of inhibitory and excitatory pathways in the globus pallidus/substantia nigra also exists.[224-227] Other researchers have reported that hand dystonia may result from cortical motor dysfunction,[228-233] degradation in the sensory thalamus,[219,234,235] disruption in cortical sensory activation, somatosensory representation or spatial perception,[178,200,202,236-241] abnormal gating of somatosensory inputs,[242] abnormal presynaptic desynchronization of movement, abnormal muscle spindle afferent firing,[233,243] or disruption of inhibition in the spinal cord.[238,244-248] Some physician scientists have evidence supporting the theory that FHd develops as a consequence of peripheral trauma, peripheral nerve entrapment, or anatomical restrictions in soft tissue.[249-256] The most controversial hypothesis is that FHd results from aberrant learning.[257]

In 1996 Byl et al.[200,202] proposed the sensorimotor learning hypothesis as one etiology of work-related FHd. According to this theory, repetitive use, simultaneous firing, coupling of multiple sensory signals, and voluntary co-activation of muscles leads to degradation of the sensory cortical representation of the hand and disruption in sensorimotor feedback.[166,176,192,193,198,202,258-261] On the basis of this hypothesis, Sanger and Merzenich[198] proposed an integrated, multisystem computational model to explain the origin of FHd. If the sensorimotor loop gain and the neural circuitry connecting the deep cortical nuclei, basal ganglia, and thalamus are unstable, a focal or a general dystonia could develop, depending on the extent of the imbalance across multiple

sensory and motor systems.[198,262] The computational model could explain why symptoms (1) develop in otherwise healthy individuals who perform highly attended, repetitive movements; (2) evolve variably in time; (3) appear only during the performance of a target-specific task; (4) (i.e., dystonic movements) persist even when the task is no longer performed repetitively; (5) decrease but are not be remediated with dopamine-depleting drugs or botulinum toxin; and (6) are associated with abnormalities in somatosensory, sensorimotor, and motor representations of the dystonic limb.

Based on the integration of the sensorimotor learning hypothesis with the computational model, appropriate treatment must reduce the imbalance in the loop gain by redifferentiating cortical and subcortical representations. If the dystonia is severe, the cycle may need to be broken temporarily with botulinum toxin injections before effective retraining can be implemented without eliciting the abnormal movements. The behavioral retraining must be based on the principles of neuroplasticity. Pathological connections must be uncoupled, and selective movements must be practiced to engage specific and relevant sensory neurons and increase coordinated movement components.

Clinical Assessment and Diagnosis

The diagnosis of FHd is made by a careful history. Past or recent trauma must both be considered risk factors,[251,255] particularly if (1) the trauma history reveals a strong temporal-anatomical relationship to the onset of FHd; (2) the trauma was severe enough to cause persistent local symptoms and lead to late medical attention; (3) the anatomical site of the original injury was the same site as the initial manifestation of the movement disorder; (4) the movement disorder developed within days or months, (up to a year) after injury; and (5) the patient had pre-existing contractures and limitations of passive movement in the area of the involved limb.[251]

FHd has also been reported in patients with a history of high stress, a recent change in levels of stress, periods of intensive repetitive hand use, job instability, application of a new technique, a change in equipment, increased time on task to improve quality of performance, and quantity of work produced or intensity of time in sports performance.[263] Most frequently, the initial complaint is pain from inflammation and swelling as a consequence of tissue microtrauma.[78,85,104,111,264] Because individuals frequently continue to perform the repetitive work, some can develop chronic pain, degenerative conditions (e.g., tendinosis),[265] fatigue, incoordination, or involuntary movements (sometimes severe cramping) when performing a familiar task.[266] Personality characteristics such as perfectionism, anxiety, stress, phobias, and emotional instability may also be abstracted from the history of those who develop a focal hand dystonia.[267,268]

On the musculoskeletal examination, the patient may complain of weakness, but unless clear signs of peripheral nerve compression are present (e.g., thoracic outlet, cubital tunnel, carpal tunnel), the muscles usually are strong. However, the patient may have a strength imbalance, with the extrinsic muscles unusually strong compared to the intrinsic muscles. Poor posture (i.e., forward head and shoulders) is common, and end range limitations may be seen in finger spread, forearm rotation, or shoulder external rotation.[269] The neurological examination should be normal (e.g., normal tendon reflexes, good coordination, stable gait, normal light touch). However, some individuals note physiological tremors, uncontrollable excitability, and possibly even some dullness or sense of numbness in the pads of the fingers when they are placed on the target surface. These patients may also perform poorly on tasks demanding cortical sensory discrimination (e.g., stereognosis or graphesthesia).[270]

During the examination, it is critical that the clinician look for abnormal movements when the patient performs the target task; this is the most objective validation of FHd. Patients should be videotaped while performing the target task, and movements should be scored for both quality and severity of aberrant movement. The Arm Dystonia Scale can be used for these ratings.[271,272] Some clinicians may be able to use computer technology or electromyography to document abnormalities of timing and force objectively.[208,256,273] It is important to examine both the involved and uninvolved limbs.[90,202,203,239,240,249,252,256,274-276]

Although not commonly ordered in the clinical setting, research studies use electrophysiological mapping, functional magnetic resonance imaging, transmagnetic stimulation, electroencephalography, and magnetoencephalography (Figures 22-10 and 22-11) to document differences in neural firing patterns, blood flow patterns with task performance, and representational topography (e.g., representational size, location, digit spread, and order).[262] Biofeedback also can be used, or involuntary co-contractions of agonists and antagonists, prolonged firing, and inability to maintain consistent firing of the dystonic muscles against resistance can be measured.

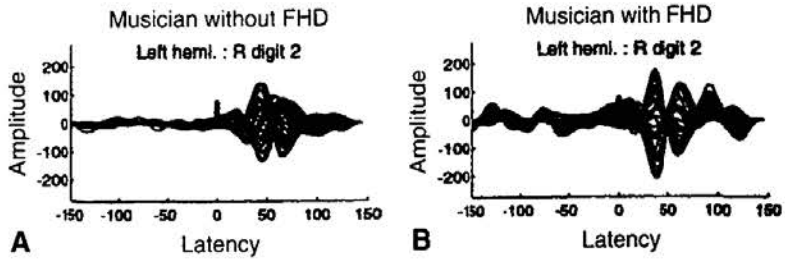


Figure 22-10

Differences in somatosensory evoked responses in a flutist without focal hand dystonia (**A**) and a flutist with focal hand dystonia (**B**). The somatosensory evoked potential for the flutist with focal hand dystonia demonstrates a short latency and a large amplitude compared to the flutist without focal hand dystonia. (From Byl NN, McKenzie A, Nagarajan SS: Differences in somatosensory hand organization in a healthy flutist and a flutist with focal hand dystonia: a case report, *J Hand Ther* 13:302-309, 2000.)

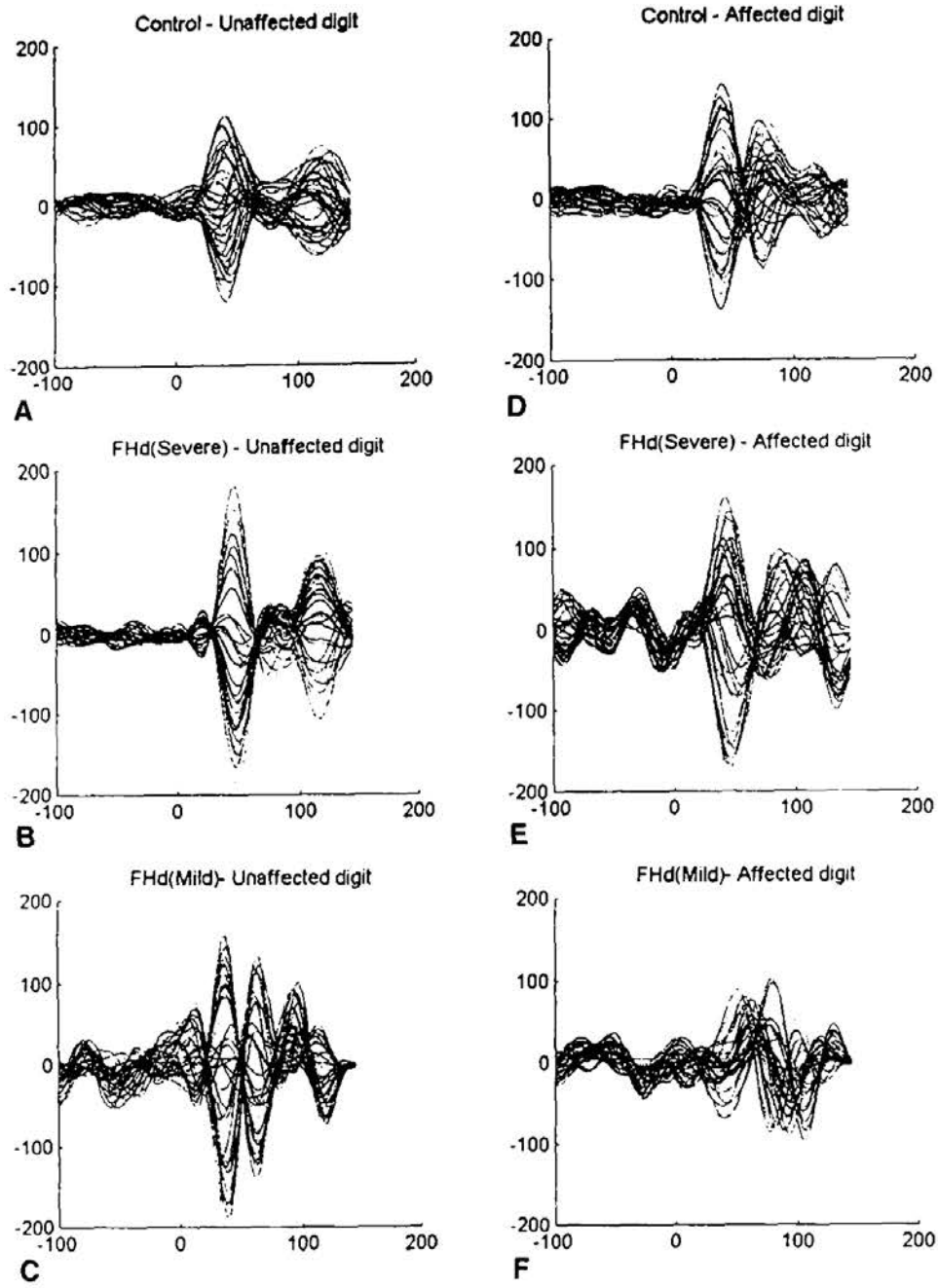


Figure 22-11
A to F, Differences in amplitude and volume over time for focal hand dystonia (FHd) subjects and controls.

Continued

General Conservative Intervention Strategies

To date, no intervention strategies are 100% effective for restoring normal motor control in patients with FHd. Injections of botulinum toxin (Baclophen) can reduce the severity of dystonic cramping by interfering with neural signals to the muscle.[213,266,277-283] Surgery may be helpful, such as nerve decompression at the elbow or wrist.[250] Surgical release of a tight retinaculum or fascia has been tried, with limited success. None of these approaches target somatosensory redifferentiation.

Conservative exercise strategies based on the principles of neuroplasticity have been tried as alternative or supplementary to medications and surgery. Some of the paradigms include constraint-induced therapy (sensory motor retuning),[284-286] sensitivity training,[287] conditioning techniques,[288] kinematic training,[289] immobilization,[290] and learning-based sensorimotor training.[169,291] Single-case studies and small prospective experimental studies have been carried out on these techniques, but none of the strategies have been confirmed by randomized clinical trials.

The strongest measure of validity for learning-based behavioral training is based on the basic scientific evidence of central nervous system plasticity, including research evidence of aberrant learning and the development of motor control problems in primates trained in repetitive task performance (see the previous section on research evidence).

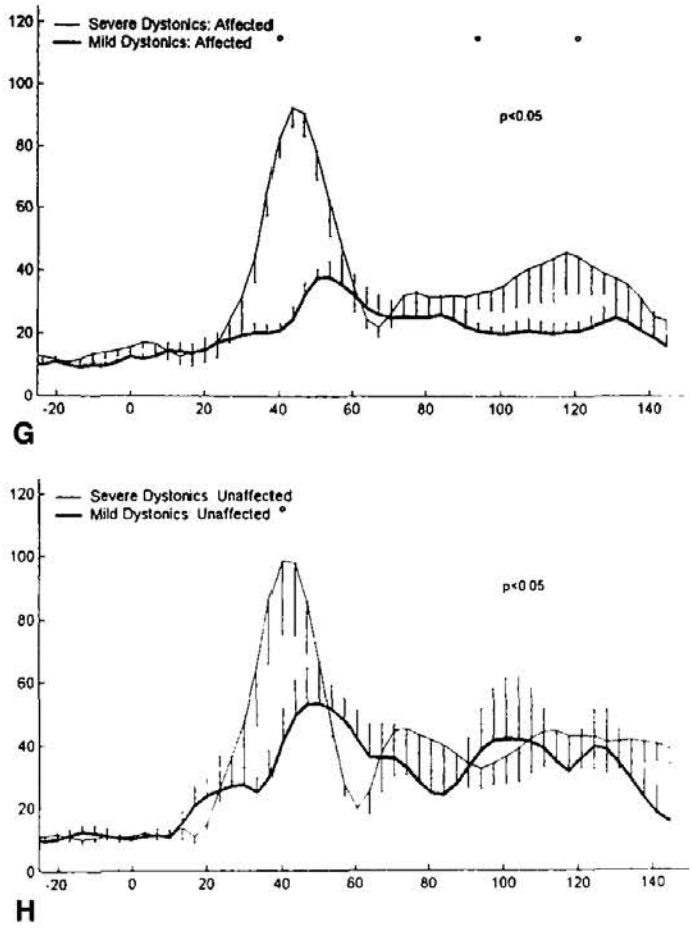


Figure 22-11 cont'd

G and **H**, Amplitude integrated by latency for FHd subjects (severe versus mild dystonia). (From Byl NN, Nagarajan SS, Merzenich MM et al: Correlation of clinical neuromusculoskeletal and central somatosensory performance: variability in controls and patients with severe and mild focal hand dystonia, *Neural Plast* 9:190, 193, 2002.)

Learning-Based Sensorimotor Training: One Treatment Approach

Box 22-1 presents the goals of learning-based sensorimotor training. Stopping the abnormal movements at both target and nontarget tasks is essential. These training activities need to take place in a positive environment for learning (Boxes 22-2 to 22-4). Specific training activities must meet the requirements for learning (Box 22-5). The patient must be educated about the neurophysiological issues surrounding dystonia and the possibility that the problem results from aberrant learning.

A critical part of the training must emphasize restoring the normal somatosensory representation of the hand in cortical areas 3a and 3b (see Box 22-5; also Box 22-6, Tables 22-6 and 22-7, and Figure 22-12). Training activities must incorporate normal sensory processing and normal movement to facilitate maximum neural adaptation. If the patient has difficulty performing the target tasks normally, imagery can be used to facilitate practice without abnormal movements. Imagery can be done mentally,

Box 22-1 Comprehensive Goals for Retraining a Patient with Focal Hand Dystonia

- Encourage the patient to think positively about recovery
- Teach the patient to stop abnormal movements
- Create a positive learning environment that meets the requisites for learning
- Teach the patient to be his or her best therapist
- Help the patient develop normal hand biomechanics and good ergonomics (integrate graded, stress-free patterns of movements)
- Quiet the nervous system (reduce hypersensitivity of muscle spindles, deep tendon reflexes, autonomic responses)
- Redifferentiate the sensory and motor representations of the hand with good sensorimotor feedback
- Restore normal graded and fine motor movements
- Practice nontarget and then target tasks at progressive time intervals
- Return to preferred work

Box 22-2 Creating a Positive Environment for Retraining/Learning: Positive Health and Fitness

- Encourage the patient to maintain good hydration (8 to 10 glasses of noncaffeinated fluids per day), balanced nutrition, and adequate sleep (7 to 10 hours per day)
- Help the patient learn how to manage stress and anxiety (workplace and personal)
- Encourage the patient to think positively about learning
- Teach the patient to avoid autonomic responses (fight/flight, cold hands)
- Encourage the patient to plan learning-based activities for each day
- Encourage the patient to participate in regular exercise:
  - General aerobic exercise program
  - Healthy movement patterns (e.g., Alexander training, yoga, tai chi, Feldenkrais, Pilates)

Box 22-3 Creating a Positive Environment for Retraining/Learning: Good Posture

- **Requirements:**

Neurological and Biomechanical Issues for Posture

- Good postural alignment with gravity
- Normal postural righting reflexes and balance
- Adequate length of muscles and fascia with good joint mobility

Education and Practice

- Teach the patient how to maintain normal excursion of neurovascular tissues.
- Help the patient develop a stable pelvis (hip abductors) and strong lower abdominal muscles.
- Teach the patient to relax the neck muscles (especially scalenes).
- Teach the patient how to breathe diaphragmatically.

Box 22-4 Creating a Positive Environment for Retraining/Learning: Positive Attitude and Commitment to Learning

- Help the patient build confidence and self-esteem
- Arrange supervised physical therapy appointments to teach the patient progressive task practice
- Educate the patient about the plasticity of the nervous system and requisites for retraining
- Encourage the patient to avoid habitual behaviors and to learn something new each day
- If the patient cannot physically complete a task, begin with the uninvolved side or use imagery
- Encourage the patient to interact with others and to get out into the community every day

Box 22-5 Requisites for Learning-Based Retraining

- Learning requires:
  - Attention
  - Reward
  - Repetition
  - Progression of difficulty
  - Small intervals of change
  - Practice spaced over time
- Learning activities should be *fun!*

Box 22-6 Requisites for Learning-Based Sensorimotor Retraining

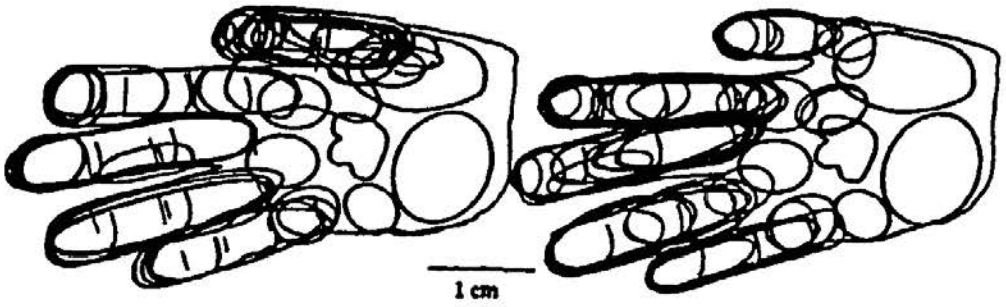
- Incorporate all sensory modalities
- Make sensory tasks and problems a forced choice condition
- Eliminate vision to focus on cutaneous information
- Attend to tactile cues to guide motor movements
- Emphasize both active and passive tasks
- Repeat a sensory task until it is performed correctly
- Determine ways for the patient to receive positive feedback:
  - Tape
  - Auditory means
  - Electrical means
  - Mirror
- Keep activities fun

having the patient focus on how the behavior looks, how it feels, and how it is controlled and executed metrically (Box 22-7 and Table 22-8).

The primary focus of the supervised sessions (1.5 hours) should be learning based sensorimotor training activities. However, as needed, the session may start with selective soft tissue, joint, and neural mobilization and nerve gliding (flossing) techniques supplemented with integrative balance activities to facilitate normal posture and recovery of pain free, normal movement. Initial sensory discrimination training should focus on the involved fingers; each finger should be individually challenged on the distal pads and then on the sides of the fingers. Sensory discrimination activities are performed with the patient in different positions (e.g., supine, sitting, or standing) to minimize abnormal movements. The sensory motor activities must include practice restoring smooth, continuous, graded movements. For example, patients are asked to lightly touch surfaces using different levels of force; this may include pressing on a scale to a specific amount or placing the hand on a turning record, the belt of a treadmill, or a portable plastic fan without stopping the movement of the record, belt, or fan blades) (Figure 22-13).

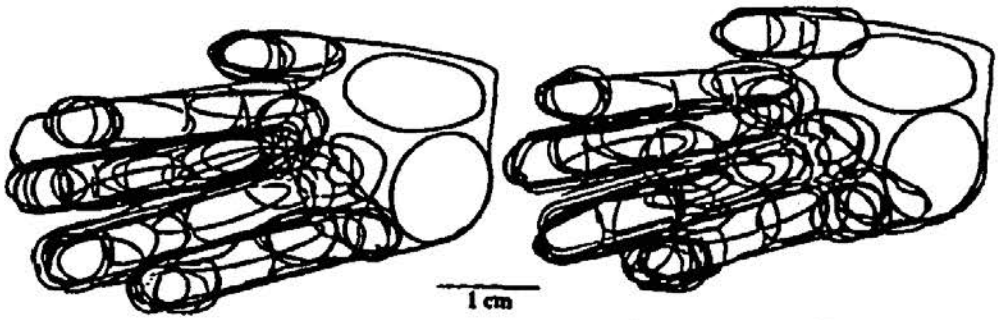
Table 22-6
Learning-Based Sensorimotor Retraining

Improve Sensory Discrimination	Improve Sensory Representation
1. Focus on sensory processing when manipulating objects 2. Use sensory (not motor) information to shape and guide movements 3. Emphasize learning activities 4. Challenge the regulation, quality, and quantity of sensory information: ○ At the initiation of movement ○ During performance of all voluntary fine motor tasks	1. Improve accuracy of separation between sensory stimuli on digits to increase differentiation 2. Increase cortical separation of digits 3. Restore digit sequence and order 4. Reduce receptive field size on digits 5. Confine receptive fields to one digit, segment, and surface



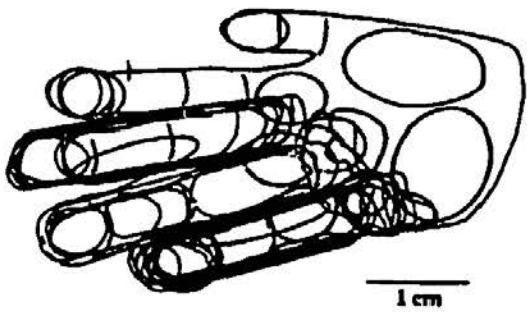
Receptive Fields Sorted by Digit 1

Receptive Fields Sorted by Digit 2



Receptive Fields Sorted by Digit 3

Receptive Fields Sorted by Digit 4



Receptive Fields Sorted by Digit 5

Table 22-7
Specific Learning-Based Training: Stereognosis and Graphesthesia

Stereognosis*	Graphesthesia†
1. Start in a position without any tension in the hand (prone, supine). 2. If tension is present in the involved hand, train with the uninvolved hand first. 3. Begin on a nontarget surface. 4. Begin sensory discrimination on the digit next to the most involved digit. 5. Begin training on the pad of the digit and then the sides of the digit. 6. Focus on one digit each day until the patient begins to notice improvement. 7. Integrate sensory exploration activities into usual activities.	1. Start with an object that is mildly sharp (e.g., a paper clip). 2. Begin in the sitting position and then change position (e.g., on the back, then arms up over the head). 3. Duplicate by having the patient draw on a piece of paper or on the skin. 4. Draw capital letters, then lowercase letters. 5. Progress from letters to figures. 6. Identify figure and proper orientation (agree to align to the tip); at 3 mm. 7. If the patient misses, repeat the stimulus up to three times and then show the patient the design. Have the patient repeat with the eyes closed and come back to it.

*Stereognosis involves active palpation and matching of objects through sensory and motor manipulation without visual cues.
†Graphesthesia involves interpreting and reproducing tactile stimuli delivered to the skin without visual cues.

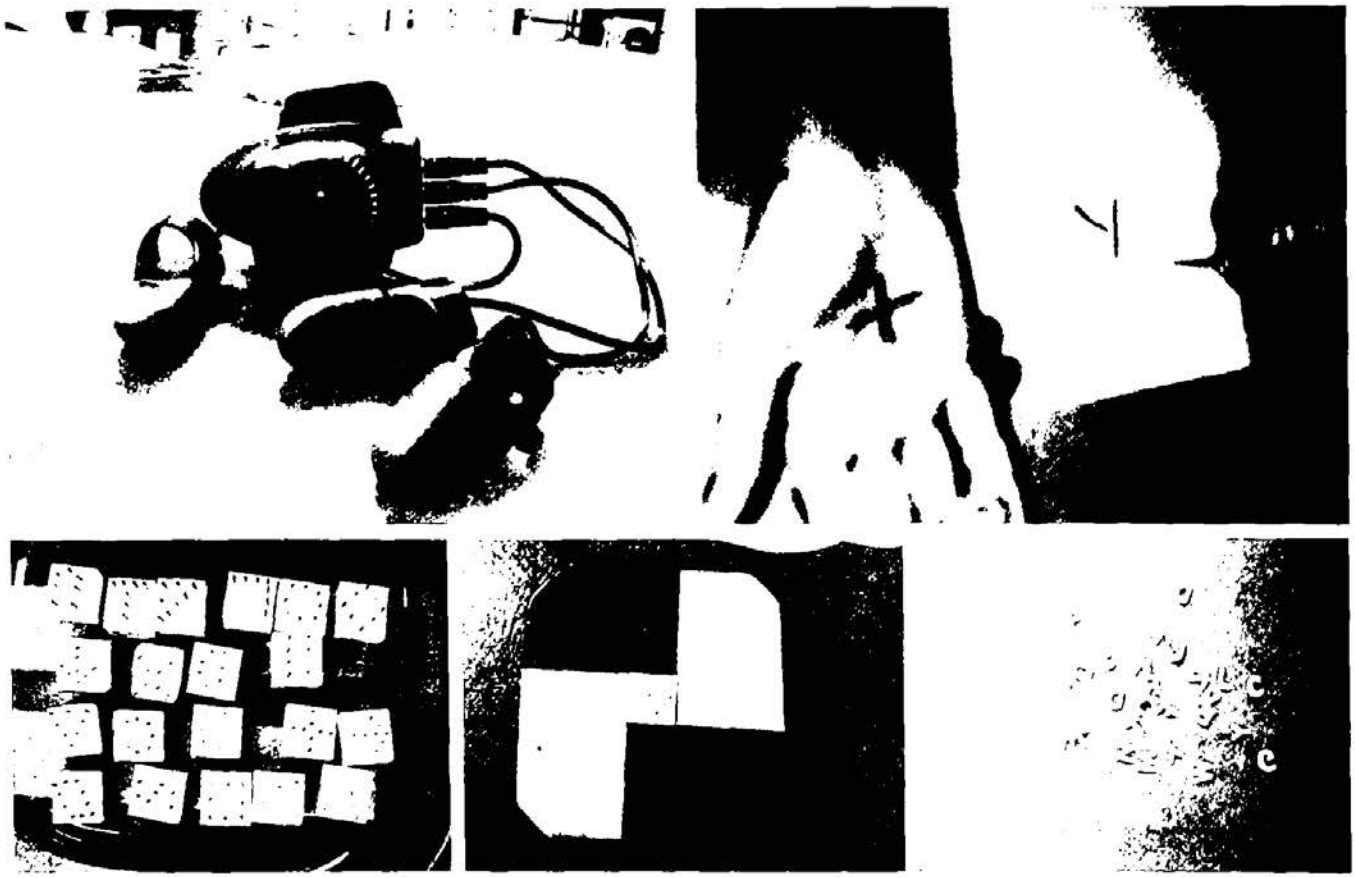


Figure 22-12
Learning-based sensorimotor training: sensory discrimination. It is important to work on redifferentiating the somatosensory cortical representation of the digits by attended, repetitive, cutaneous tasks targeted at each involved digit. Examples of some tasks patients are asked to practice are shown.

Box 22-7 Incorporating Imagery into Sensory and Motor Training

- Have the patient mentally go back in time to when the task could be performed smoothly and normally with control
- Break down the functional task into small tasks
- Have the patient place the fingers on the target instrument and feel the instrument
- Have the patient drop the hand to the instrument from the elbow
- Have the patient move up and down on the instrument using shoulder movement
- Have the patient mentally rehearse and practice moving normally
- Have the patient imagine the motor, sensory, and visual aspects of the task
- Supplement imagery with brief practice periods on the target task

Table 22-8
Reinforcing Learning with Imagery

Relaxation	Mental Rehearsal and Practice
• Find a quiet place with no interruptions • Take a few minutes to relax • Imagine being in a special comfortable place	• Mentally practice performing the target task without pain or abnormal movement • Remember the positive feelings of performing your work, sport, or hobby

As part of the sensorimotor retraining program at home (at least 1 hour per day), the patient must think about the sensory aspects of using the hands rather than the motor aspects of task performance. The patient is instructed to let the sensation of the object shape the hand. To get positive feedback, the patient can place the unaffected hand in front of a mirror with the affected hand behind the mirror (Figure 22-14). This allows the patient to use the mirror image (looks like the affected hand) to guide normal movement of the affected digits and hand. When the mirror is used, the objects need to be exactly the same and must be placed in the same position on both sides, which requires placing the object in the same position as the mirror image for the affected side. Patients also should be instructed to use biofeedback for retraining (e.g., place tape on the involved fingers to increase sensory input and control range of movement or use auditory biofeedback to minimize co-contractions of agonists and antagonists) (Figure 22-15).

The patient should be encouraged to find a video of someone performing the target task normally or to view a video made before the dystonia was a problem. While watching the video, the patient should imagine that the hands on the video are their hands. As sensory processing skills improve, the patient is asked to place the hands on the target instrument and simply feel the instrument. When the hand can be placed on the instrument without abnormal movement, the individual is instructed to practice small, independent, isolated movements of the uninvolved and involved digits for short periods, repeated and spaced throughout the day. When returning to instrumental

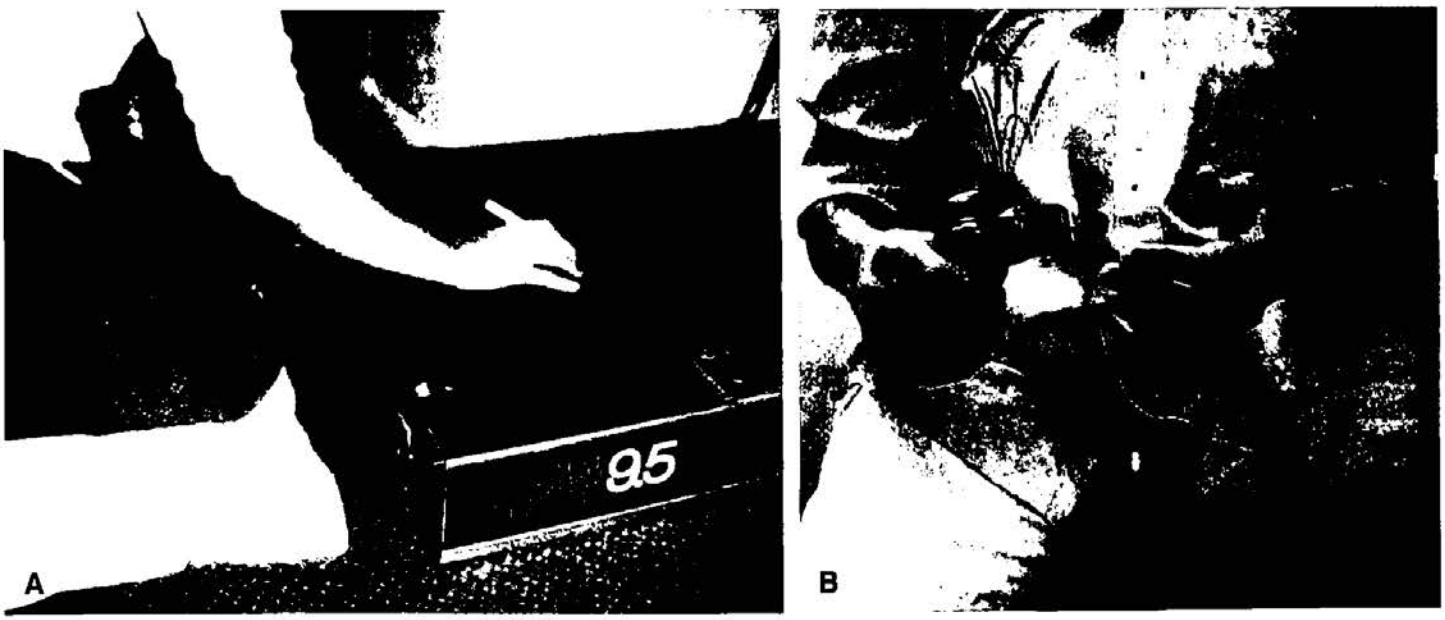


Figure 22-13
Learning-based sensorimotor training: graded movement. When the agonists and antagonists contract simultaneously, performing fine motor tasks is difficult. Creating situations in which a patient has to maintain light contact on a moving object without interfering with the movement of the object can be challenging. Two examples include placing the hand on the treadmill (**A**) and having the fingers lightly touch the soft blades of the fan without stopping the fan (**B**).

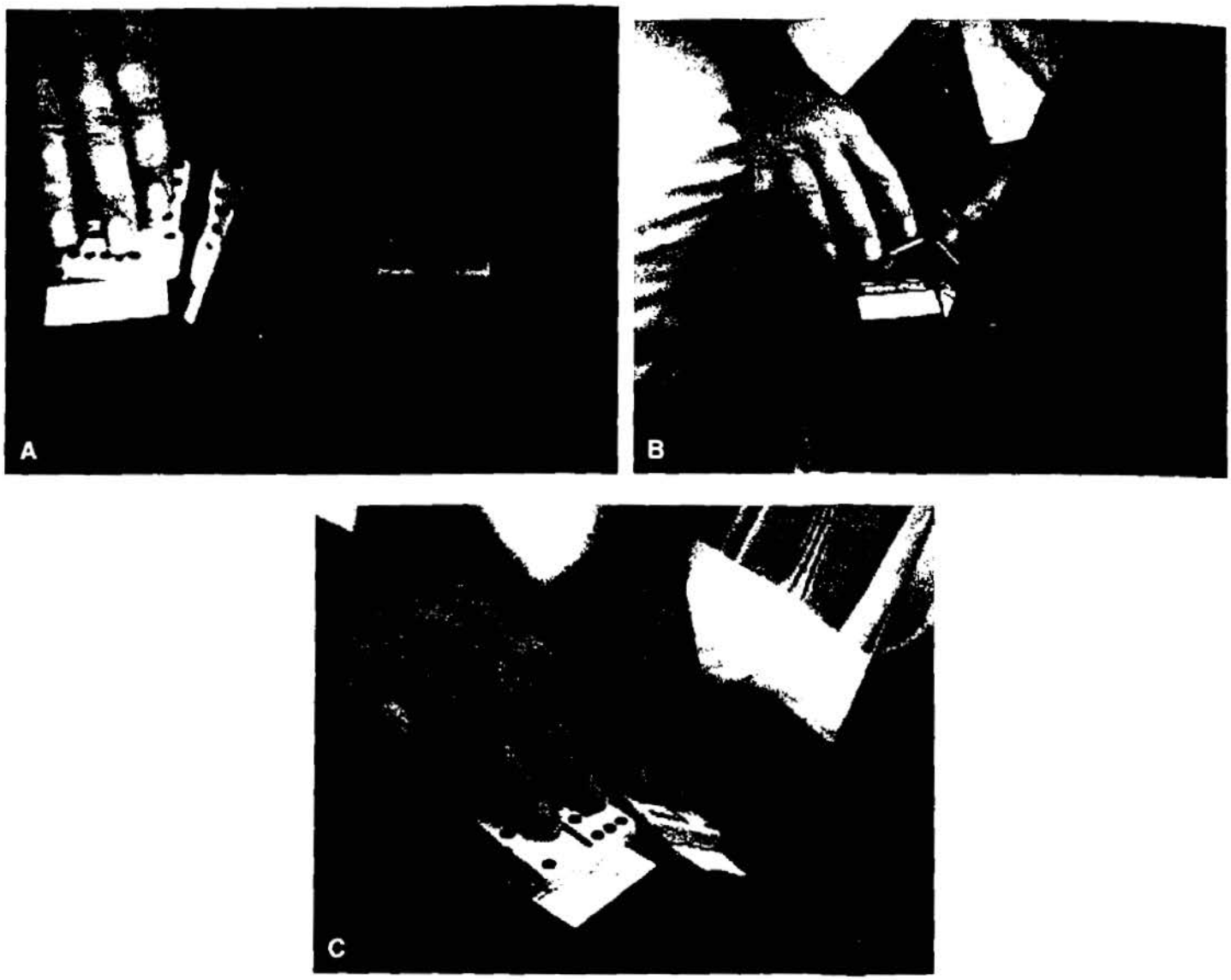


Figure 22-14
Using mirrors to enhance feedback. **A,** The mirror image of the unaffected limb looks like the affected hand. **B,** The patient is asked to place the affected hand behind the mirror and then copy the mirror image in either a sensory or a motor task. If another person is watching, that individual can give feedback or guide the hand behind the mirror. **C,** The patient matches dominos in the mirror with dominos felt behind the mirror.

practice, the patient needs to begin with new music, not established protocols.

Research Evidence for Aberrant Learning: Repetitive Overuse of the Limb as One Origin of Focal Hand Dystonia

Primate Studies

The evidence supporting the theory of aberrant learning in repetitive strain injuries and FHd comes from both animal and human studies. The initial studies were carried out with normal nonhuman primates trained to perform stressful repetitive hand tasks. The animals eagerly trained on a daily basis for juice or pellets. The animals trained for up to 1.5 hours a day. In one case they trained by opening and closing a handpiece and in another case by trying to meticulously place the thumb and the index finger on two points. A recording electrode was placed over the dura of the somatosensory cortex in one primate to record responses to tactile inputs to the hand. This allowed the researchers to monitor dynamic change in cortical representation and changes in motor performance. Training sessions were videotaped, and performance data were controlled by LabView virtual instrument software.

Five of seven primates trained until they could no longer perform the task. They began to have difficulty either closing or opening the hand on the target task. In addition, their training rate slowed, and they were not accurate. When their speed was less than half the initial training speed, the primates were placed under anesthesia and a careful topographical map of the hand was characterized using electrophysiological mapping techniques. The

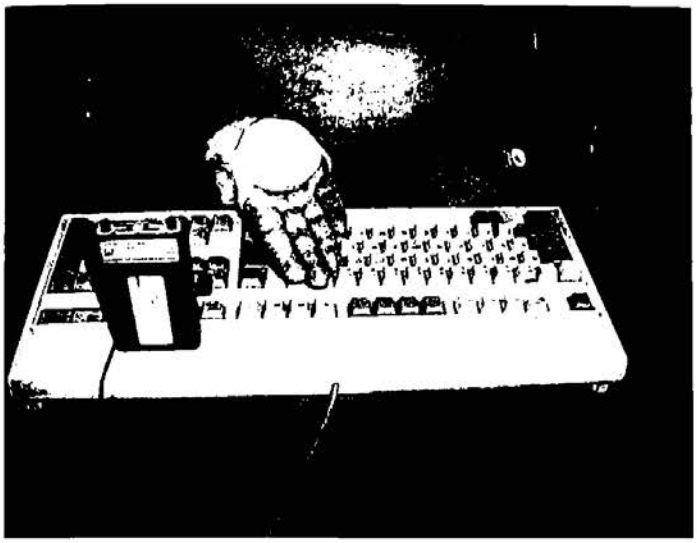


Figure 22-15
Use of biofeedback to reinforce learning. Patients must learn to use the small muscles inside the hand, rather than the long finger flexors and extensors, to move the digits. In this example, the patient tries to restore a round palm and depress the keys using the muscles inside the hand instead of the long finger flexors. The biofeedback fires when the extrinsic muscles of the forearms are used.

topography of the digits and the palm was mapped using MAP 50 software,[296] and the receptive fields for each digit were drawn for each cortical penetration. The details of anesthesia, surgery, and electrophysiological monitoring met the criteria for safety and have been reported in a variety of studies.[166,168,171,182 186,192,200,202,292]

The normal topography of the hand is characterized with one receptive field per electrode penetration, small receptive fields ($8 \pm 3\ mm^2$) unique to each digit, orderly sequencing of digits from inferior to superior and segments from proximal to distal, distinct differentiation of the digits at 100 to 600 μm, and an area of representation of 3.2 to 5.1 mm^2 (see Figure 22-8).[183,186,295,299] With learning-based training, the area of representation increases in size, whereas the receptive fields decrease in size. In addition, specificity and density increase.

A normal primate has a precise somatosensory representation of the hand (see Figure 22-9); however, the trained monkeys showed a significant dedifferentiation of the somatosensory hand representation on the trained side. Mild dedifferentiation was seen on the untrained side. Multiple receptive fields were recorded per cortical penetration, with frequent overlapping of receptive fields across adjacent digits and across glabrous and dorsal surfaces. The receptive fields were significantly larger than normal ($p < 0.0001$ compared to normal), and the areas of the cortical hand representations were significantly reduced on the contralateral hemisphere of the trained monkeys ($p < 0.001$, respectively, compared to normal). A breakdown in the normally separated cortical representations of different digits also was seen, with overlapping of receptive fields ranging up to a cortical distance of 2000 μm on the trained side (see Figure 22-9).

The mean size of the digital receptive fields was significantly larger than in controls on the trained side. Most of the cortical penetrations had multiple receptive fields, and the receptive fields frequently overlapped the segments on a single digit, adjacent digits, or dorsal and glabrous surfaces (respectively different from controls $p < 0.0001$). For the monkey with only one dystonic finger (D4), the dense mixing of hairy and glabrous surfaces occurred only for the one isolated digit. When receptive field overlapping was plotted as a function of cortical distance, normal monkeys had minimal overall overlapping of the receptive fields across 600 μm, whereas the monkeys with FHd had overlapping receptive fields up to 2 mm (whether performing the active or passive task). The hand representations were mildly degraded on the untrained side as well, with some but less extensive overlapping of receptive fields with adjacent digits or glabrous and dorsal surfaces.

Interestingly, in the primate with the implanted electrode, the changes in the topography could be monitored as physical performance deteriorated. The electrode had been implanted over digit 1 (D1) and digit 2 (D2). However, as performance deteriorated, the receptive field sizes of D1 and D2 increased, as did the overlapping of receptive fields as the duration of training time increased. As training continued, the medial face expanded into the hand representation of D1 and D2. This area of the face was consistent with a cortical columnar substitution.

After mapping, anatomical dissections of the dystonic and nondystonic hands showed no signs of acute inflammation.[254] One monkey had a congenital defect of the flexor superficialis and flexor profundus on the fourth digit on the trained side and the third finger on the untrained side. This monkey developed uncontrollable extension of D4 after 4 weeks of training. No signs of movement dysfunction were seen on the left, untrained side. The receptive fields on this hand were larger than normal but did not overlap across adjacent or dorsal and glabrous surfaces.

Two primates trained very slowly and casually right from the start. They took a lot of breaks and would work only for 20 to 30 minutes. They also would lean back with the trunk rather than squeeze the handpiece. These two primates did not have sufficient repetitive, stereotypical, or coincident movements to exceed the integration time of each contact or repetitive movement; therefore no aberrant learning and no topographical degradation of the hand representation were seen.

Human Research Models

McKenzie et al.[239] and Byl et al.[257,291,300,301,304,305] carried out a variety of clinical studies to gather more evidence supporting the sensorimotor learning–based hypothesis for FHd. The goals of this series of experiments were (1) to describe the neurophysiological and clinical correlates of patients with FHd (Experiment I); (2) to outline the differences in sensorimotor function by severity of FHd

(Experiment II); (3) to evaluate the effectiveness of learning-based sensorimotor training in remediating FHD (Experiment III); and (4) to relate change in clinical function to change in cortical structure after a learning-based sensorimotor retraining program (Experiments IV and V).

All the subjects who participated in the studies (healthy controls and those with hand dystonia) worked in an occupation that demanded repetitive use of the hands. The subjects in the experimental groups had a history of chronic repetitive strain injury and were recruited primarily from the Peter Ostwald Health Program for Performing Artists and the Physical Therapy Faculty Practice at the University of California, San Francisco. Males and females 20 to 60 years of age who lived in the San Francisco Bay area (or were willing to come to the area for treatment) were eligible. All subjects were referred by a neurologist, hand surgeon, or occupational medicine or primary care physician.

Each subject had been clinically diagnosed with FHd at least 6 months before participating in the study. Each demonstrated (1) observable involuntary twisting movements of the digits and wrist when performing the target or similar tasks; (2) normal reflexes; and (3) no evidence of objective peripheral neuropathy or central nervous system pathology. The subjects had not received an injected or systemic drug to control the dystonia for more than 6 months before admission to the study. Ten subjects with FHd and 15 controls were recruited for Experiment I; 17 subjects with FHd and 17 controls were recruited for Experiment II; 12 subjects with FHd and 30 controls were recruited for Experiment III; one case study was used for Experiment IV; and three case studies were used for Experiment V.

Subjects with FHd were classified as having simple or dystonic dystonia. Simple dystonia was defined as dystonia limited to one target task; dystonic dystonia was defined as dystonia that occurred with tasks similar to the target task or surface contact of the hand. Severity was established according to the Tubiana Dystonia Scale for Musicians (*0*, unable to do the target task; *1*, able to do limited aspects of the task or perform the task for very short periods; *2*, able to do the task with modification of technique; *3*, able to do the task but not efficiently or with normal quality).[287]

For Experiment I, the subjects with FHd were classified into one of two severity categories, mild or severe. Those with simple dystonia demonstrated at a single task (rated 0 or 1) were classified as mild dystonia, whereas those with dystonia when performing multiple tasks were rated 2 or 3 and classified with severe dystonia.

Control subjects were contacted from a previous data base of healthy subjects. These subjects were age and gender matched to serve as historic reference controls for each of the experimental studies. In Experiment I, 15 reference controls were included; 17 controls were included in Experiment II. In Experiment III, 30 reference control subjects were included.

A broad battery of standardized clinical tests was administered to the experimental and control groups. The test procedures and the reliability of testing have been described in previous studies and are summarized in Table 22-9.[202,239,270,274,275,301,302] Somatosensory testing was performed by trained research assistants according to standard protocols. Specific subtests were summed into seven dependent variables: (1) physical musculoskeletal performance (selected range of motion, strength, neural tension); (2) sensory discrimination (graphesthesia, localization, kinesthesia, stereognosis); (3) fine motor efficiency (Purdue Test time), fine motor skill (line tracing accuracy and time), and digital reaction time (averaged across the five digits for each hand); (4) motor control at the target task; (5) posture and balance; (6) functional independence; and (7) pain. The subtests allowed for comprehensive measurement of clinical performance.[301]

Magnetoencephalography was used to define the neurophysiological responses to sensory stimuli. Each test was performed by a trained staff member in the laboratory and interpreted by professionals trained in bioimaging.[302,303] The test-retest values for the magnetic source image (MSI) testing established in this laboratory are high (>0.9).[178] A 37-channel biomagnetometer (Magnes II, 4D Neuroimaging, 1.5 fT, San Diego, CA) placed in a magnetically shielded room with two circular sensors (14.4 cm) was used to create a Magnetic Source Image of the hand. Two hundred fifty air puffs were delivered within 1 cm^2 sacs, for 30 milliseconds (msec), at 17 to 20 pounds per square inch (psi), with a pseudorandom interstimulus interval of 450 to 500 msec. The stimulus was a superthreshold force designed to indent the skin 400 μm. Each digit on each hand was stimulated on the distal pad, the middle segment, and the proximal segment. In addition, a similar stimulus was delivered to each side of the upper lip.

Normal cutaneous somatosensory evoked field (SEF) responses are characterized by a peak amplitude at a latency between 30 and 70 msec, subject to a signal to noise ratio greater than 4, goodness of fit (model/data) greater than 0.95 with a minimal confidence volume less than 3000 mm^3.[302-304] The dependent variables recorded for each SEF response included latency (in milliseconds), root mean square (rms) amplitude across sensor channels (fT), ratio of amplitude to latency, location of the digits on the *x*, *y* and *z* axes (in centimeters), spread between digits, order of the digits on the *z* axis, and volume of the hand representation ($4/3\,\Pi$ times the radius of the spread on the *x*, *y* and *z* axes).

Experiments I and II: Correlation of Clinical Performance and Neural Structure. In Experiment I, 10 subjects were admitted to the study (19 to 60 years of age, primarily musicians). Fifteen subjects served as reference controls. Most of the controls were graduate students whose lives involved intensive computer use and writing.

Table 22-9
Summary of Clinical Testing Procedures

Measurement Tool	Dependent Variable	Scoring System	Directions	Reliability	Equipment
Graphesthesia (modified subtest of Sensory Integration Praxis Test [SIPT])	Sensory performance	2 = Correct 1 = Partially correct 0= Incorrect % error calculated	Tip of a paper clip was used to draw designs on subject's fingers while eyes were closed (EC). Subject recreated design with pen with eyes open (EO). Two designs per finger pad.	Inter-rater = 0.95 Test-retest: r = 0.91 (Ayres[311])	Paper clip and design sheet
Kinesthesia (subtest of SIPT)	Sensory performance	Average error (distance from target) in mm	Subject's hand was moved to target and back to start position; subject attempted to relocate digit, EC. Five trials per hand.	Inter-rater = 0.95 Test-retest: r = 0.90 (Ayres,[311] Byl et al.[270])	Target sheet and ruler
Byl-Cheney-Boczai Test (BCB) for stereognosis	Sensory performance	2 = Correct 1 = Partially correct 0 = Incorrect % error calculated	Subject's finger was drawn across the shape twice, EC. Subject attempted to pick correct shape. Ten trials for second and fourth finger pads.	Inter-rater/intrarater = 0.995 (ICC) Correlation of r = .60 b/w BCB (Byl et al.[312] and Purdue Test Lafayette Instruments)	Twenty designs and test sheet of designs
Digital reaction time	Fine motor performance	Time in msec, average of all trials	Subject turned stopwatch on/off as quickly as possible. Three trials per finger.	Intrasession reliability ranges from 0.975-0.99 (Bohannon[313])	Stopwatch
Purdue Test	Fine motor performance	Total time to put pegs in and out	Subject put 25 pegs into a board and then removed them.	Lafayette Instruments - distributer	Watch, peg-board
Manual muscle test	Musculoskeletal performance	Kilograms of force: UE and LE Scores total all scores*	Performed per procedures defined by Kendall (Kendall and McCreary[314]) with dynamometers added to increase objectivity used for grip, key, and pinch grip.	R = 0.887 Multiple correlation with manual muscle test (MMT)	Jamar, Microfet, and Baseline dynamometers

(Continued)

Table 22-9
Summary of Clinical Testing Procedures—Cont'd

Measurement Tool	Dependent Variable	Scoring System	Directions	Reliability	Equipment
Range of motion	Musculoskeletal performance	Degrees; sum of active and passive	Performed measurement procedures defined by Norkin (Norkin and Levangie[315]). Arm, wrist, and hand joints summed to an UE score, and joints in the leg summed to a LE score and then totaled.	Intratester: r =0.91-0.99	Goniometer
Posture and balance	Postures and balance	Ordinal scales: 2 = Fully met criteria 1 = Partially met criteria 0 = Did not meet criteria	Posture: Bony landmarks cited for line of gravity (Kendall and McCreary[314]) were coded as 0-2 and summed to a total. Balance score summed from: Feet together (EO and EC for 20 sec), one foot (EO and EC for 10 sec), and tandem Romberg (EO and EC for 10 sec).		
CAFÉ 40	Functional performance	7-point Likert Scale: 1 = Least independent 7 = Most independent	Self-scoring of ability to perform functional activities. Scores inverted for data analysis.	Test-retest: r = 0.971 (Fung et al.[316])	Written questionnaire

Companies supplying instruments (including administration guidelines): (1) Hogan Health Industries, Microfet Dynamometer: Medical Products division, Hogan Health Industries, Inc.; (2) Jamar Dynamometer: TEC, 60 Page Road, Clifton, New Jersey 07012; (3) Lafayette Instrument Company: Instructions and Normative Data, Purdue Pegboard, P.O. Box 5729, Lafayette, Indiana 47903, 1996; and, (4) Finger Tapper: Psychological Assessment Resources Inc. P.O. Box 998, Odessa, Florida 33556.

UE, Upper extremity; *LE*, lower extremity.

*Muscle groups tested: Hip flexors and extensors, knee flexors and extensors, ankle dorsiflexors, elbow flexors, shoulder flexors, wrist extensors, lumbricals, grip and pinch (3-jaw chuck and key grip) strength.

In Experiment II, nine males and eight females with FHd were admitted (23 to 55 years; mean age, 39.9 years [± 11.1 years]). All worked in jobs requiring repetitive hand movements (e.g., musicians, computer users). Eleven of the FHd subjects had simple dystonia, and six had dystonic dystonia. Ten subjects could no longer practically perform the target task such as writing, keyboarding or musical performance (severe dystonia), and seven could perform the task for short periods with modification of technique (mild dystonia). Fifteen reference control subjects (eight males and seven females) were included, ranging in age from 23 to 57 years, with a mean age of 37.4 years (± 9.7 years). Two controls were musicians, and the other subjects worked aggressively on a computer keyboard. Most of the control subjects were graduate students, faculty, or friends of students or faculty who had a history of repetitive hand use (e.g., intensive note taking and computer use).

In both experiments I and II, subjects with FHd performed significantly worse than healthy controls when using either the affected or unaffected side on musculoskeletal tasks, balance activities, postural alignment, fine motor control, and sensory discrimination. In Experiment II, in a comparison of the affected limb, those with severe dystonia demonstrated greater restrictions on musculoskeletal skills and target-specific motor control. Although the overall sensory discrimination accuracy was low for all FHd subjects, those with severe dystonia performed faster than those with mild dystonia. On the unaffected side, those with mild dystonia demonstrated greater inaccuracy when performing the target-specific task (see Figure 22-11).

No significant differences were seen between the mean SEF latency or mean amplitude for FHd subjects and reference controls in either study, but the location of the digits on the x axis (bilateral) and the y axis (affected) were significantly different ($p < 0.0001$, respectively), and the ratio of SEF mean amplitude to latency was higher for FHd subjects compared to controls ($p \leq 0.05$) (see Figure 22-11). On the unaffected side, the volume of the hand representation was significantly larger for FHd subjects compared to controls ($p < 0.05$).

In Experiment II, the ratio of SEF amplitude plotted by response latency was significantly lower in the early phase (less than 100 msec) for the FHd subjects compared to controls. The amplitude was similar for the control subjects and the FHd subjects for the unaffected digits on the affected limb and the digits on the unaffected limb. In addition, in Experiment II subjects with FHd showed a bimodal distribution of mean SEF amplitude plotted by mean latency on the affected side (mean latency ranging from 30 to 60 msec and the mean amplitude ranging from 20 to 119 fT). A negative linear trend of amplitude by latency was seen for the digits on the unaffected side for FHd subjects and all of the controls (as the latency increased, the amplitude decreased).

The field evoked firing patterns for controls and those with dystonia (mild and severe) were similar when measured on an unaffected part, the lip. However, in Experiment II, integrating amplitude by latency on the affected limb, those with severe dystonia had a significantly higher amplitude than those with mild dystonia. Those with severe dystonia had a short latency and a high amplitude, and those with mild dystonia had a long latency and a low amplitude (see Figure 22-11). Bilaterally, the volume of the representation of the hand for those with mild dystonia was larger than the volume for subjects with severe dystonia.

High, significant correlations (0.9029 affected and 0.8477 unaffected; $p < 0.001$, respectively) were seen between the severity of dystonia and the SEF ratio of amplitude to latency. On the affected side, negative correlations were seen between the SEF ratio and dystonia severity with musculoskeletal performance, motor control on the target task, and fine motor skills. FHd subjects with mild dystonia tended to have a low SEF ratio and demonstrated higher performance on these tasks than those with severe dystonia. A significantly negative correlation was seen between fine motor skills and the SEF ratio on the affected side; those with a high SEF ratio of amplitude to latency demonstrated greater inaccuracy. On the unaffected side, a significant, moderately positive correlation was seen between the severity of dystonia and performance on the target task; subjects with mild dystonia had lower performance scores on the target task.

Experiment III: Effectiveness of Intervention with Learning-Based Sensorimotor Training. The purpose of this study was to assess the effectiveness of learning-based sensorimotor training and recovery of task-specific and sensory motor function in patients with FHd.[169,291] Twelve subjects met the same criteria summarized in Experiment I and completed the clinical tests as described in Experiment I. The principles of treatment are summarized in Boxes 22-1 to 22-7 and Tables 22-6 to 22-8 and discussed in the previous section describing learning-based sensorimotor training.

All subjects improved significantly on all parameters of clinical performance (25% to 80%), bringing the performance of musculoskeletal parameters, sensory discrimination, and fine motor control to the level of normal subjects. Task-specific motor control increased to 94%. All but two subjects returned to their previous work, but none regained 100% control of the hand, Rather, each subject had to be careful with performance strategy, reducing tension and implementing careful ergonomic strategies. Some subjects no longer played professionally, although others returned to professional performance.

Experiments IV and V: Effectiveness of Learning-Based Sensorimotor Training. The purpose of the case reports used in experiments IV and V was to determine the effect of learning-based sensorimotor training on

neurophysiological and structural change and clinical function in patients with FHd. One subject with work-related keyboarder's cramp and three musicians were included in the studies. Ten healthy, age-matched subjects served as reference controls for magnetoencephalography, and 30 additional healthy subjects served as reference norms for the clinical performance parameters. Two subjects lived outside the United States, and two were from the San Francisco Bay area. All the subjects agreed to participate in at least 8 weeks of physical therapy. All the subjects had been diagnosed with FHd by a neurologist approximately 1 year before this current intervention study.

All the subjects were otherwise healthy except for complaints of painless, uncontrollable curling of digits four and five (D4-D5) on the left hand when they played their instrument. All the subjects described excessive curling or extension of D5 and difficulty lifting D4. All subjects noticed that controlling D4 and D5 was more difficult when D3 was pressing down. All the subjects were completely independent in personal care and household management and were well integrated into the community. These subjects followed the learning-based sensorimotor training paradigm, in addition to going to the gym to maintain a positive fitness routine.

All the subjects participated in measurements before and after treatment, including magnetoencephalography and clinical testing as described in experiments I and II.[90,169,179,202,257,291] Subject 1 participated in supervised treatment for 12 weeks (two 6-week sessions), subject 2 participated daily for 2 weeks, and subjects 3 and 4 participated in therapy once a week for 17 weeks. Consequently, the total period of treatment and the number of visits with a physical therapist varied across subjects (23 visits for subject 1, 19 visits for subject 2, and 23 to 25 visits for subject 3).

At baseline, controls had a similar pattern of somatosensory evoked responses on the right and left sides, with one exception: on the *z* axis, the spread of the digits on the dominant hand was greater than on the nondominant hand. In addition, on both hands the order and location of the digits on the *z* axis followed a predictable pattern, with D2-D5 progressing from inferior to superior. However, subjects with FHd demonstrated measurable differences. The amplitude and spread of the somatosensory evoked responses of the digits on the *x*, *y*, and *z* axes were reduced on the affected side compared to the unaffected side, and the digits were not sequentially organized from inferior to superior for D1-D5 on the *z* axis on either side. Compared to controls, the musicians with FHd had a shorter SEF latency, the neuronal burst was higher on the affected and unaffected sides for subjects 1 and 3, and the amplitude was lower in the early phase (30 to 70 msec) for subjects 2 and 3. The location of the hand representation on the *x*, *y*, and *z* axes were different for FHd subjects and controls, and bilaterally, the spread of the digits on the *x*, *y*, and *z* axes was greater for the subjects with FHd (who were all musicians) compared to controls.

In general, the reference controls achieved comparable clinical performance bilaterally and across digits, except that motor reaction time was slower for digits 4 and 5. Some of the controls had postural asymmetry and indicated that their health sometimes interfered with daily activities (scoring 89.6% of a maximum score of 100% for functional independence). On the other hand, at baseline, on both the affected and unaffected sides, the subjects with FHd demonstrated reduced accuracy and slowing in sensory processing compared to controls. On the motor performance tests, subjects 1 and 3 performed bilaterally with reduced motor accuracy and had prolonged processing time. On the affected side, Task Specific Motor Control Scores were approximately 50% lower than on the unaffected side. Subjects 2 and 3 had limited finger spread between D3 and D4 and D4 and D5 on the affected side (25° on the affected side compared to 35° to 45° on the unaffected side). Compared to controls, the subjects with FHd were more likely to have poor posture, positive signs of neurovascular entrapment, decreased strength in the lumbricals (on both sides), and limited shoulder internal rotation (e.g., 45° to 55° bilaterally). All of the subjects with FHd returned to school or work but were not working at their usual jobs. They still reported difficulty with target-related functional activities (scores ranging from 63% to 90% of maximum performance compared to an average of 89.6% for controls).

Based on repeated magnetic source imaging, mapping did not change with retesting in controls. However, the three subjects with FHd showed a general increase in the spread of the digits and the area of representation on the cortex on the trained side (larger than control subjects), whereas a decrease in the area of representation was measured on the unaffected side. On the affected side, the order of the digits (D1-D5) approximated an inferior to superior progression from D1 to D5, but the digits were less distinctly ordered than in controls (Figure 22-16). The amplitude of the evoked somatosensory potential, integrated over time, was increased and similar to controls on the affected side (see Figure 22-16; also Figure 22-17).

After intervention, the subjects with FHd scored between 80% and 90% on the target task. Motor reaction time was similar to controls on the affected and unaffected sides. The subjects with FHd improved 37% to 42% in motor accuracy, performing similarly to controls; however, they needed more time to complete each task. Accuracy improved 25% to 50% on all sensory tests (e.g., they performed similarly or better than controls). However, two of the subjects with FHd required more time to perform the tests compared to controls (e.g., 66-197 seconds compared to 37 seconds for controls). The subjects with FHd

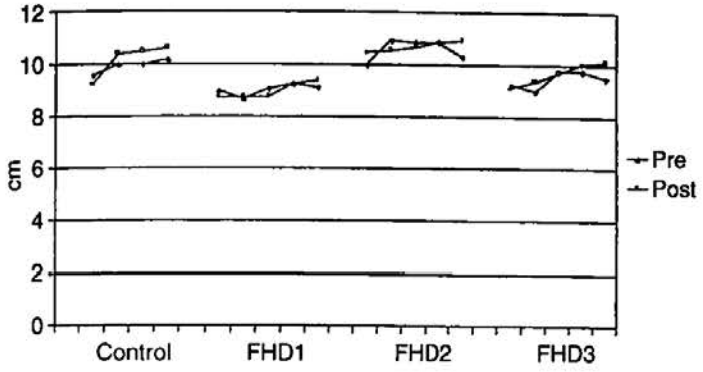


Figure 22-16
Improvement in somatosensory mapping with training: sequence of digits. With learning-based sensorimotor training, the sequential representation of the digits was improved. (From Byl NN, Nagajaran S, McKenzie AL: Effect of sensory discrimination training on structure and function in patients with focal hand dystonia: a case series, *Arch Phys Med Rehabil* 84:1508, 2003.)

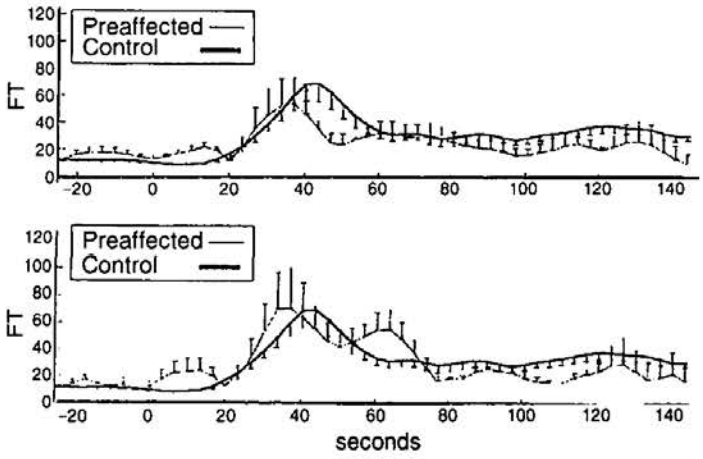


Figure 22-17
Improvement in somatosensory evoked field responses after training. With learning-based sensorimotor training, the somatosensory evoked response improved. When the evoked magnetic field response was mapped over time, an increase in the amplitude similar to controls was seen. (From Byl NN, Nagajaran S, McKenzie AL: Effect of sensory discrimination training on structure and function in patients with focal hand dystonia: a case series, *Arch Phys Med Rehabil* 84:1508, 2003.)

achieved similar flexibility, strength, and posture compared to controls.

Table 22-10 presents a summary of the findings of clinical experiments I to V.

Summary

FHd is a complex movement disorder that primarily affects the hand. It can develop when a person repetitively overuses the upper limb. This condition may arise because the brain is overly adaptive. Both animal and human studies showed a degradation in the somatosensory representation of the hand but no signs of local acute inflammation. Clinical studies indicate that patients with FHd with a history of repetitive overuse of the hand also show a variety of musculoskeletal and neuromuscular limitations compared to healthy controls. Learning-based, sensorimotor training produced objective improvements in clinical function and neural structure, strengthening the evidence indicating that neuroplasticity combined with aberrant learning is one etiology of FHd. However, within the limits of current reimbursement mechanisms, the intervention may not be rigorous enough to achieve 100% recovery.

Behavioral training programs that are progressively repetitive, attended, and rewarded are critical to the process of shaping voluntary, high quality, controlled, fine motor movements. Although the theoretical evidence supports the likelihood that aberrant learning is one etiology of FHd, controlled, randomized clinical trials are needed to better define the parameters of intervention and to maximize neural adaptation.

Conclusion

In U.S. industry, musculoskeletal disorders account for 1 in 3 workdays lost as a result of injuries or illness. Strong epidemiological evidence indicates that a major risk factor for the development of work-related MSDs of the upper limb is the performance of hand-intensive tasks that are highly repetitive or forceful (or both) in awkward or sustained postures and/or in conditions involving vibration, cold temperatures, or both. Psychosocial stress also increases workers' risk of developing overuse injuries of the upper limb, as do co-morbid medical conditions and other risk factors not related to the workplace. Multidisciplinary workplace and clinical management programs that follow a biopsychosocial model are the most effective approaches to treatment of these disorders.

Most of the impairments that arise with overuse injuries occur because of local tissue microtrauma. The peripheral tissue damage can be treated effectively with anti-inflammatory medication, rest, and work modifications. The movement dysfunction known as focal hand dystonia can be a secondary complication of excessive overuse of the hands. This problem is difficult to treat because it leads to changes in the central nervous system rather than the peripheral nervous system. In these cases, the individuals who successfully rehabilitate are those who can stop the activities that generate the abnormal movements. These patients then need to learn how to use healthy biomechanical strategies to perform hand tasks stress free. A positive environment, including stress management, good ergonomics, wellness, and fitness, must be created before patients engage in specific, learning-based, sensorimotor retraining strategies to reorganize the somatosensory maps of the hand. Differentiated digit representations are essential to the performance of normal

Table 22-10
Summary of Findings: Clinical Experiments I-V

Parameter	Findings
Differences in neuromusculoskeletal performance: controls and subjects with functional hand dystonia (FHd)	1. Subjects with FHd performed significantly worse than healthy controls when using either the affected or unaffected side on musculoskeletal tasks, balance activities, postural alignment, fine motor control, and sensory discrimination. 2. Subjects with severe dystonia demonstrated: ◦ Greater restrictions on musculoskeletal skills and target specific motor control ◦ Reduced accuracy in sensory discrimination, but they performed faster than those with mild dystonia ◦ Better sensory discrimination accuracy on the unaffected side compared with subjects with mild dystonia (see Figure 22-11)
Somatosensory evoked field responses: controls and subjects	1. No significant differences were seen between the mean somatosensory evoked field (SEF) response latency and the mean amplitude for FHd subjects and reference controls. 2. The locations of the digits on the x (bilateral) and y axes (affected) were significantly different ($p < 0.0001$, respectively), and the ratio of SEF mean amplitude to latency was higher for FHd subjects compared to controls ($p < 0.05$) (see Figure 22-11). 3. On the unaffected side, the volume of the hand representation was significantly larger for FHd subjects compared to controls ($p < 0.05$). 4. The ratio of SEF amplitude plotted by response latency was significantly lower in the early phase (<100 msec) for the FHd subjects compared to controls. 5. The amplitude was similar for the control subjects and the FHd subjects for the unaffected digits on the affected limb and the digits on the unaffected limb 6. There was a bimodal distribution of the mean SEF amplitude plotted by mean latency on the affected side (mean latency ranging from 30-60 msec and the mean amplitude ranging from 20–119 fT). 7. There was a negative linear trend of amplitude by latency for the digits on the unaffected side for FHd subjects and all of the controls (as the latency increased, the amplitude decreased). 8. The field evoked firing patterns for controls and those with dystonia (mild and severe) were similar when measured on an unaffected part (i.e., the lip). 9. Integrating amplitude by latency on the affected limb, those with severe dystonia had a significantly higher amplitude than those with mild dystonia. 10. Subjects with severe dystonia had a short latency and a high amplitude and those with mild dystonia had a long latency and a low amplitude (see Figure 22-11). 11. Bilaterally, the volume of the representation of the hand for those with mild dystonia was larger than the volume for subjects with severe dystonia.
Correlation of magnetoencephalography (MEG) and clinical performance parameters	1. High, significant correlations were seen (0.9029 affected and 0.8477 unaffected; $p < 0.001$, respectively) between the severity of dystonia and the SEF ratio of amplitude to latency. 2. On the affected side, negative correlations were seen between the SEF ratio and the severity of dystonia with musculoskeletal performance, motor control on the target task, and fine motor skills. 3. FHd subjects with mild dystonia tended to have a low SEF ratio and demonstrated higher performance on these tasks than subjects with severe dystonia. 4. A significantly negative correlation was seen between fine motor skills and the SEF ratio on the affected side; those with a high SEF ratio of amplitude to latency demonstrated greater inaccuracy. 5. On the unaffected side, a significant, moderately positive correlation was seen between the severity of dystonia and performance on the target task; subjects with mild dystonia had lower performance scores on the target task.

Table 22-10
Summary of Findings: Clinical Experiments I-V—Cont'd

Parameter	Findings
Change in neurophysiological structure and physical function after training	1. All subjects improved significantly on all parameters of clinical performance (25% to 80%), bringing the performance of musculoskeletal parameters, sensory discrimination, and fine motor control to the level of normal subjects. 2. After the intervention, the subjects with FHd scored between 80% and 90% on the target task. 3. Motor reaction time was similar to controls on the affected and unaffected sides. 4. The subjects with FHd improved 37% to 42% in motor accuracy, performing similarly to controls; however, they needed more time to complete each task. 5. Accuracy improved 25% to 50% on all sensory tests, a performance similar to or better than controls. However, subjects with FHd required more time to perform the tests compared to controls (e.g., 66-197 seconds compared to 37 seconds for controls). 6. Subjects with FHd achieved flexibility, strength, and postural alignment similar to that of controls. 7. All but two subjects returned to their previous work, and none gained 100% control of the hand; each subject had to be careful with his or her performance strategy, reducing tension, and implementing careful ergonomic strategies. Some subjects were no longer playing professionally, but some had returned to professional performance. 8. Based on repeated magnetic source imaging, mapping did not change with retesting for controls. For subjects with FHd: ◦ A general increase in the spread in the area of representation was measured on the unaffected side. ◦ On the affected side, the order of the digits (D1-D5) approximated an inferior to superior progression from D1 to D5, but the digits were less distinctly ordered than controls (see Figure 22-17). ◦ The amplitude of the evoked somatosensory potential, integrated over time, was increased and similar to controls on the affected side (see Figures 22-16 and 22-17).

fine motor movements. This retraining must be attended, carefully graded and progressed, rewarded, and spaced over time; it also should be self-directed in the home setting. The training must be interesting, engaging, and fun for the patient. Computerized instrumentation (e.g., goal-oriented, game-formatted learning paradigms) may enhance the effectiveness of retraining.

References

To enhance this text and add value for the reader, all references have been incorporated into a CD-ROM that is provided with this text. The reader can view the reference source and access it online whenever possible. There are a total of 316 references for this chapter.

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