Learning-based Animal Models: Task-specific Focal Hand Dystonia

Nancy N. Byl

Abstract

Dystonia is a disabling, involuntary disorder of movement that leads to writhing, twisting end-range movements or abnormal postures. Inadequate inhibition could account for excessive excitation and near synchronous co-contractions of agonists and antagonists. Dystonia may be generalized or specific, affecting only one part of the body or involving only a well-learned task (e.g., writing, keyboarding, golfing, playing a musical instrument). Task-specific and other focal dystonias are considered idiopathic, with multiple factors such as genetics, anatomy, physiology, psychology, environment, and behavioral characteristics contributing to the development of symptoms. This article provides detailed descriptions of two behavioral animal models (a primate [owl monkey] model and a rodent [Sprague-Dawley rat] model) developed to study the effect of excessive repetition as a potential etiology of focal hand dystonia (FHd). The hypothesis is that repetitive, near simultaneous hand movements can degrade the topographic representations of the hand on the somatic sensory and motor cortices, creating the involuntary movements characteristic of dystonia. While animal studies permit the opportunity for greater control to determine efficacy, the findings must always be confirmed by clinical studies to evaluate sensitivity and specificity of diagnosis and effectiveness of treatment in the home, work, and personal environment. This article presents a review of the etiology and clinical implications for intervention strategies from animal and clinical studies that support learning-based mechanisms for FHd. Other animal models are also briefly reviewed.

Key Words: focal hand dystonia; neuroplasticity; repetitive hand use; somatosensory mapping; task-specific hand dystonia

Introduction: Sensory and Motor Foundations of Movement

Because most hand tasks require delicate, complex, individuated, fine motor movements (Gerloff et al. 1998; Johansson 1996; Sherrington 1947), the hand has large, orderly, somatotopic, highly differentiated representations in the thalamus, basal ganglia, and cortex (Figure 1; Iwamura et al. 1983; Iwamura 1992; Jenkins et al. 1988; Kass et al. 1983; Penfield and Rasmussen 1950; Wang et al. 1994, 1995). Integrative functional representations of well-learned tasks such as riding a bike, walking, and writing (Rijntjes et al. 1999) complement these topographic representations.

In the course of a human life, maturation and development, environmental enrichment, deprivation, drugs, disease, injury, and attended, practiced progressive behaviors can modify the topographic and functional neural representations in the brain (Byl and Merzenich 2000; Hasselmo and Bower 1993; Hasselmo 1996; Hikosaka et al. 1984; Jenkins et al. 1990a,b; Wang et al. 1994, 1995). Learning upregulates neurotransmitters such as dopamine and acetylcholine (Gil et al. 1997; Juliano et al. 1991; Karne 1995), generating selective changes in synaptic processing to differentiate and selectively specialize representations that create more efficient, accurate, and differentiated behaviors (Merzenich and deCharms 1996; Merzenich and Jenkins 1995; Merzenich et al. 1996; Recanzone et al. 1992a,b,c).

The outcomes of progressive mental and physical practice have been measured in terms of changes in structure such as:

- expanded cortical representations,
- smaller receptive fields,
- narrower columnar specificity,
- coselection of complementary inputs,
- increased number of excitable neurons,
- enhanced salience and specificity of feedback,
- increased myelination,
- strengthened synapses between coincident inputs,
- shortened integration time, and
- increased complexity of dendritic branching.

Outcome studies on neuroplasticity have used both animal models (Allard et al. 1991; Elbert et al. 1995; Hebb 1949; Jenkins and Merzenich 1987; Jenkins et al. 1988, 1990a,b; Kaas et al. 1983; Merzenich 1990; Merzenich and

Metabolic state, sleep, and natural endorphins can heighten and refresh good neural networks while emotions such as worry, depression, stress, fear, and anxiety can erase poor connections, create negative connections, or block learning (Byl and Merzenich 2000). In addition, competition between neuronal pools, time constants, integration time, and reflex inhibition can limit neural adaptation (Byl and Merzenich 2000; Sanger and Merzenich 2000). When inputs occur near simultaneously in the inhibitory or integration period, distinct registration of information may be lost (Gerloff et al. 1998; Merzenich et al. 1999; Wang et al. 1995). The stimulated skin surfaces form a unified rather than a unique representation in the cerebral cortex (Byl et al. 1996c, 1997) and the borders of the digit representation are broken down (Bara-Jimenez et al. 1998, 2000; Blake et al. 2002; Chen and Hallett 1998; Pascual-Leone et al. 1995b; Sterr et al. 1998; Wang et al. 1994, 1995; Woolsey 1958). Thus, excessively practiced, precise, attended, repetitive, rapid, stressful, nearly coincident hand movements can negatively affect somatosensory and motor topography and ultimately impair motor control (Bara-Jimenez et al. 1998; Blake et al. 2002; Byl et al. 1996c, 1997, 2000b; Nudo et al. 2000; Wang et al. 1994, 1995). Spatial and temporal separateness of noncoincident inputs and distinct digital borders are essential to the maintenance of normal sensory organization and fine motor control of the hand, particularly during the acquisition of new motor movements (Gerloff et al. 1998; Pascual-Leone et al. 1995a). The impact of these topographical changes in the presence of cortical hyperexcitability and poor inhibition can exaggerate motor control problems (Butefisch et al. 2005; Bohlhalter et al. 2007).

**Basic Interaction and Neurophysiology of Sensory and Motor Systems**

The ascending sensory pathways include peripheral receptors, dorsal column nuclei, the ventral posterolateral thalamic nucleus, and primary somatosensory cortex area 3b. As the ascending pathways project from one level to the next, there is modality preservation, with separation of connectivity between groups of neurons that carry different types of response properties. In particular, neurons that respond to stimulation of hairy skin do not mix in functional connectivity with neurons that represent glabrous skin; neurons that represent different fingertips do not mix; and neurons that respond only to deep skin stimulation do not mix with those that respond to light cutaneous stimulation. Thus neurons respond either to one modality or another, but not both.

Researchers have observed modality preservation in multiple levels of the nervous system (Gordon and Paine 1960; Johnson et al. 1992; Kruger et al. 1961; McComas 1963; Millar and Basbaum 1975; Perl et al. 1962). Neurons, which cluster in the dorsal columns in small modules (0.5 mm in diameter), all respond to the same stimulation modality and are similar in positional representation on the skin surface (Dykes et al. 1982). This precise representation exists in the primary thalamic nucleus for the somatosensory inputs (the ventral posterolateral nucleus). Early neuronal recording studies confirmed the specificity of the anatomi-
Focal Hand Dystonia

Focal hand dystonia (FHd\textsuperscript{1}), also referred to as occupational hand cramps, task-specific dystonia, writer’s cramp, musician’s cramp, golfer’s yip, or keyboarder’s cramp, is one type of focal limb dystonia (Altenmueller 1998). The writhing and twisting movements of dystonia interfere with normal task-specific motor control (Altenmueller 1998; Bell 1883; Cohen and Hallett 1988; Cole et al. 1995; Fry 1986; Hochberg et al. 1990; Jankovic and Shale 1989; Marsden and Sheehy 1990; Newmark and Hochberg 1987; Rothwell et al. 1983; Tubiana 1998; Tubiana and Chamagné 1983; Uitti et al. 1995). Although FHd is considered idiopathic, the etiology is thought to be multifactorial. Even with a familial gene for dystonia (e.g., the DYT1 gene in cervical torticollis), movement dysfunction does not develop in all carriers. Rather, the disorder presents (phenotype) in the presence of a combination of genetic, anatomic, personality, behavioral, and stress-related challenges to the nervous system. Although hand dystonia is one of the most common types of focal dystonia, blepharospasm (involuntary spasms of bilateral eyelid closure) and spasmodic torticollis (sustained involuntary muscle contractions that rotate the head into abnormal postures) are also common focal dystonias, in which researchers report problems in sensorimotor integration, cortical excitability, and loss of inhibition (Evinger 2005; Sohn and Hallett 2004; Sohn et al. 2002).

There are no clinical laboratory tests to diagnose FHd. Rather, clinical diagnosis depends on a careful history, patient-reported signs and symptoms, and a physical examination that includes a detailed neurological examination with nerve conduction velocity studies and observation of the movement dysfunction during performance of the target task. Magnetic resonance imaging (MRI) usually shows that the brain of patients with focal dystonia is normal in structure. Sensory and motor mapping with magnetoencephalography and functional magnetic resonance imaging (fMRI) are not usually included as part of the clinical diagnostic process. For research purposes, these imaging techniques are useful for documenting differences in firing patterns, areas of activation, and the topography (e.g., representational area size, location, digit order, latency, amplitude, density of neural firing, and co-contractions of agonists and antagonists) (Byl et al. 2000c, 2002; Pujol et al. 2000). Electrophysiological mapping under anesthesia also reveals abnormal firing in the globus pallidus and the thalamus (Lenz and Byl 1999), not just the sensory and motor cortices.

In addition to the disorder in movement, patients with FHd may complain of increased sensitivity, jumpiness, or a hand tremor when performing specific tasks. Some individuals experience movement irregularities when they just think about performing the target task or simply place the pads of the fingers in contact with the target surface. Some also complain of a “dullness or numbness” or hyposensitivity (decreased awareness and sensitivity of sensory inputs) of the involved digits (Byl et al. 2002).

No intervention strategies are 100% effective for restoring normal motor control in patients with FHd. The most common interventions are pharmaceutical, and include systemic medications to decrease the tremor (Baclophen) or sedate the nervous system, or local injections of botulinum toxin to block the unwanted contractions of the involved muscles (Brin et al. 1987; Ceballos-Baumann et al. 1995; Cole et al. 1995; Fahn et al. 1987; Karp et al. 1994; Pullman...
et al. 1996; Tsui et al. 1993; Van Hilten et al. 2000). Surgery is occasionally recommended for severe limb dystonia (e.g., implantation of electrical stimulators in the globus pallidus for patients with severe cervical torticollis) (Uitti et al. 1995). Other treatment options are conservative, behavioral intervention strategies based on the principles of neuroplasticity. These paradigms include constraint-induced therapy (sensory motor retuning; Candia et al. 1999, 2002, 2003), sensitivit training (Tubiana et al. 1998), conditioning techniques (Liversedge and Sylvester 1955, 1960), kinematic training (Mai and Marquardt 1994), immobilization (Priori et al. 2001), Braille reading (Zeuner and Hallett 2003, Zeuner et al. 2002), and comprehensive learning-based sensorymotor training (Byl and Merzenich 2000; Byl et al. 2000a,c). A better understanding of the etiology of FHd could lead to more directed and specific prevention and intervention strategies.

The Benefits of Animal versus Clinical Models for Studying Hand Dystonia

A number of clinical, descriptive, genetic, and imaging studies of patients with FHd have elaborated descriptions of the physiological and anatomical characteristics of patients with dystonia. Investigators have documented changes in neural topography with electrophysiological mapping in patients with dystonia who are having surgery. However, it would of course be unethical to create the movement disorder in healthy human subjects in order to study the etiology of dystonia. Thus researchers need animal models to study the possible metabolic, genetic, environmental, and behavioral origins of dystonia. On the other hand, it is difficult to create animal intervention models based on complex, fine motor, or cognitive learning–based behavioral training paradigms.

Several animal models do, however, exist for studying the etiology of dystonia. Some involve injecting drugs into selected neurons or areas of the brain. But while drugs may create various disorders of movement, the resulting disorder does not necessarily simulate human patients with a genetic or behaviorally induced dystonia. For this reason, studies of movement disorders commonly use behavioral animal models.

Investigators have developed in vivo primate models (Blake et al. 2002; Byl et al. 1996c, 1997) and in vivo rat models (Barbe et al. 2003, 2005; Barr and Barbe 2002, 2004; Barr et al. 2004; Clark et al. 2004) to study the etiology of FHd. The hypothesis for the primate studies was that high levels of repetitive, near simultaneous movements would lead to central somatosensory changes in the topography of the hand that would ultimately interfere with normal movement control. The initial hypothesis at the beginning of the rat studies was that high levels of repetition would lead to local and systemic inflammation and ultimately cellular degradation. With continued training, however, the animals showed movement dysfunctions that had not been expected.

Primate Models of Focal Hand Dystonia

Experiment I (Tasks A and B)

Subjects. Four adult owl monkeys (Aotus nancymaeae) and reference controls from other research studies (Jenkins et al. 1990a,b; Recanzone 1992a,b,c)

Training task. The monkeys were trained to perform one of two hand-closing tasks (Figure 2). In Task A, the primate placed the hand on a handpiece that passively opened and closed the hand for variable periods of time. In Task B, the monkey placed the hand on the instrument and then had to actively close and open the hand for a variable number of repetitions. Two monkeys were trained on Task A and two on Task B.

Training Procedures

The monkeys were introduced to the tasks in the home cage in the animal care housing facility, where their behavior was shaped progressively until they were able to perform in a consistent, stereotypic manner. First, the monkeys learned how to reach for food through a controlled opening. Once they learned this behavior, they trained 5 days a week at the Keck Center for Integrative Neuroscience in a cage mounted in a sound-isolated test chamber, with a video system outside the cage monitoring their behavior. A short cylinder mounted on the cage front guided the monkey to reach to a handgrip in a mid-range vertical position. The handgrip was molded to fit the monkey’s hand, with contact detectors on the thumb piece and each finger groove. The

Figure 2 Sensorimotor training apparatus designed to engage an adult monkey in the repetitive exercise of active opening and closing of the hand. Reprinted with permission from Byl NN, Merzenich MM, Cheung S, Bedenbaugh P, Nagarajan SS, Jenkins WM. 1997. A primate model for studying focal dystonia and repetitive strain injury: Effects on the primary somatosensory cortex. Phys Ther 77:269-284.
monkeys were deprived of food for 20 to 22 hours before beginning each training week (with weight maintained at 80% to 90% of normal). For behavioral rewards a pellet feeder attached to the side wall of the cage provided nutritionally complete, whole-grain, banana-flavored pellets of 45 mg (Bio-Serv, Frenchtown, NJ) or Tang. The monkeys received water ad libitum and food supplements after training.

In the passive task (A), the monkey’s digits had to make contact with the detectors on the handpiece to activate a spring-loaded device that opened and closed the handpiece while positioned in the monkey’s hand. A second spring-loaded solenoid, mounted on the thumb pad, opened and closed the thumb. The excursion of the fingers was 6.44 mm and the thumb plate 1.5 mm. The openings occurred quickly (within 16 milliseconds) and closure required approximately 50 milliseconds.

In the active opening and closing paradigm (Task B), a spring-loaded solenoid in the handpiece provided a known force (80 g) against which the monkey had to squeeze over a distance of approximately 7 mm in order close the instrument. When the handpiece was completely closed, it vibrated. When the vibration stopped, the monkey had to quickly release contact by extending the fingers, at which point the handpiece automatically reopened. Both tasks were controlled by LabView® virtual instruments software (Byl et al. 1996c, 1997) and were

- attended,
- rapid,
- rewarded,
- stereotypical and near coincident in time,
- repetitive (for 2 hours a day, 5 days a week), and
- practiced over time (5 weeks to 12 months).

Speed of repetitions, number of repetitions, time of training, and accuracy of task performance were monitored with Labview®. After motor performance deteriorated by 50% in speed and accuracy, training continued at least another 2 weeks before mapping was carried out. These protocols were approved by the UCSF Committee on Animal Research.

**Surgery and Electrophysiological Monitoring**

Anesthesia was induced with a 1.5% halothane, 75% N₂O/25% O₂ gas mixture to allow for placement of a venous catheter. The monkeys were then anesthetized with sodium pentobarbital given to effect (initial dose, 28 mg/kg IV), and intravenous supplementation maintained the monkeys at a surgical level of anesthesia. Blood pressure and heart rate were monitored. With 5% dextrose, a lactated Ringer’s solution was continuously infused intravenously (6 ml per hour) and adjusted according to hydration. Temperature was maintained at 38°C and the bladder was emptied at regular intervals. The animals were maintained areflexic throughout the experiments. Every 24 hours, atropine sulfate was given along with penicillin G (30,000U). The experiment was performed using sterile surgical procedures and the animals were kept in a pain-free state.

The electrophysiological mapping was performed according to standard techniques that have been reported in detail by other investigators (Jenkins et al. 1990a; Merzenich et al. 1983a,b, 1984; Petersen and Merzenich 1995; Recanzone et al. 1992a,b,c; Stryker et al. 1987; Wang et al. 1994, 1995). The anesthetized monkey was mounted in a stereotactic apparatus and a wide craniotomy exposed the anterior parietal cortex centered on S1 cortical area 3b. With the dura resected, a well for sterile, high-viscosity silicon oil was constructed. A Sony CCD camera recorded a computer image of the cortex and the hand.

Parylene-coated tungsten microelectrodes with 1- to 3-Ohm impedances (at 1 kHz) were used as the recording electrodes. All penetrations were parallel to one another and introduced roughly perpendicular to the cortical surface. Data were collected at a depth of 700 to 800 microns below the cortical surface corresponding to deep cortical layer 3 in area 3b. Single-unit and multiple single-unit recordings were amplified, bandpass filtered, and displayed by the use of conventional methods, then fine-tipped, opaque glass probes were used to define each cortical penetration. The stimulus was defined as a just-visible indentation. Reference studies reported just-visible indentations in the area of 250 to 500 microns, the middle of the dynamic range of large-fiber cutaneous mechanoreceptor afferent fibers.

MAP 50 software (Petersen and Merzenich 1995) was used to reconstruct the cortical representations and to measure the cutaneous receptive fields (Petersen and Merzenich 1995; Phan and Recanzone 2007; Recanzone and Becker- man 2004). The penetration site was marked on a photograph of the cortex, and the receptive field(s) for each sample neuron(s) carefully drawn to scale on the computer hand image by using a mouse cursor in the cortical mapping software (Blake et al. 2002, 2005a; Stryker et al. 1987). When receptive fields overlapped into different functional hand surfaces, cortical representational boundaries were drawn. One monkey was mapped for 15 hours and recovered. Three monkeys, mapped for up to 5 days with 24-hour monitoring, hydrating, and medicating according to the standards required by the committee on animal care, were not recovered.

Investigators have also used MAP 50 software (Petersen and Merzenich 1995) to construct and measure the cortical representation and to measure the size of the cutaneous receptive fields. The clinical dependent variables included motor performance on the target task and the food retrieval task (Labview® virtual instruments collected accuracy and speed measurements, and videotape captured quality of movement). Both of the movement paradigms were scored for quality. Two evaluators assigned ordinal values of task performance at the beginning and end of the training with the mean values used for analysis. In a preliminary study, the intraclass correlation coefficient (ICC) for the reliability of rating on the movement scale was > 0.99 (Byl et al.
1996c). After the topographical mapping, the animal was sacrificed and anatomic dissections were taken of the median and ulnar nerves and of the flexor and extensor tendons in both the trained and untrained hands. The purpose of the anatomic samples was to compare the levels of inflammatory cells, fibroblasts, and macrophages in the affected and unaffected hands to determine whether the movement anomalies might be related to acute inflammation or scarring in the trained, movement-impaired hand.

Data Analysis

This was a one-group, pre- and post-test design with reference controls. Although the number of animals was small, we gathered over 100 days of data on motor accuracy and frequency of task performance, and mapped 300 to 400 receptive fields for each monkey. Dependent variables measuring clinical performance included accuracy, speed, and quality of food retrieval task performance. For the electrophysiological data, we mapped the area of the topographical field, calculated the total area, plotted the cortical distances and the number of receptive fields per electrode penetration, counted the number of overlaps across adjacent digits and across glabrous and dorsal receptive fields, and calculated the circumference of the receptive fields. We used the Page test to analyze the decline over time in performance speed and accuracy on the trained side, and for comparisons between the trained animals and the controls we used the Wilcoxon Two-Sample Test. Each of the dependent variables was considered an independent family (with independent measurements) and tested for significance at p < 0.05 (Marascuilo and McSweeney 1977). The presence of inflammatory cells and fibroblasts was documented after anatomical dissection and immunochemical analysis as part of the secondary analysis, and plotted for visual trend analysis.

Results

Task A: Passive hand opening. Two owl monkeys performed the attended, repetitive, passive hand opening and closing task for 1.5 to 2 hours a day, 5 days a week, for 12 to 25 weeks. Initial performance was 90% accurate. After 5 to 8 weeks, both monkeys experienced difficulty removing their hand from the handpiece and reduced the number of trials performed. After a period of low work rate, one monkey resumed the prior intensity of task performance for 4 weeks and then began having difficulty placing the second and fourth digits on the handpiece, dropping to less than 50% accuracy. However, after the period of reduced intensity of work, the second monkey resumed the gripping behavior for another 3 months and then developed difficulty keeping the hand on the handpiece, with a decrease in accuracy of performance to less than 50%. Task frequency decreased from 15 to 16 trials per minute to 9 trials per minute. The monkeys continued to perform the task for another 2 weeks after the observation of abnormal movements and poor task performance.

We expected the somatosensory hand organization to have one receptive field per electrode penetration, with each receptive field (RF1) unique to each digit, the digits sequenced from one to five from inferior to superior, and the segments of the digits ordered from proximal to distal (Figure 1). For the monkeys trained on the passive task, electrophysiological mapping revealed significant dedifferentiation of the somatosensory hand representation on the trained side. The areas of the cortical hand representations on the contralateral side of the trained hand were 1.3 mm² and 1.98 mm² compared to a range of 3.2 to 5.2 mm² for normal owl monkeys (p < 0.001) (Stryker et al. 1987). The receptive fields on the hand were very large (Figure 3). Many of the cortical penetrations had multiple receptive fields and they frequently overlapped adjacent digits or dorsal and glabrous surfaces (Figures 4 and 5). While the mean RFs for this primate species (Aotus nancymae) averaged 8.0 ± 3.0 mm², the RFs on the hands of the two trained monkeys were significantly larger than normal (78.0 ± 22.5 mm² and 150.4 ± 237.5 mm² (p < 0.0001). The dedifferentiation was illustrated by a breakdown in the normally separated cortical representations of the different digits. Occasional overlap of digital representations has been documented in normal owl monkeys along a cortical distance of

![Figure 3](http://ilarjournal.oxfordjournals.org/)
100 to 600 microns (Recanzone et al. 1992a,b,c), but in the trained monkeys, the RF overlap was documented up to a cortical distance of 2,000 microns (Figure 6). There were also mild signs of degradation on the untrained side.

**Task B: Active hand opening.** After shaping to perform the active hand opening and closing, the two monkeys temporarily decreased the repetition of task performance in the third week of training. This temporary rest was interpreted to suggest possible pain from excessive repetition. But both monkeys resumed training after a week. Interestingly, one monkey continued to use an articulated strategy of opening and closing the hand and the second monkey changed the strategy of performing the task.

After 24 weeks of training, the monkey using the articulated strategy decreased both the task frequency (from 16 trials per minute to 7 trials per minute; p < 0.001) and task accuracy (by more than 50%). At the same time, motor control in both the target and food retrieval tasks deteriorated. The somatosensory organization of the hand was seriously degraded on the trained side (Figure 7), with many receptive fields overlapping adjacent digits (Figure 8). The mean size of the digital receptive fields was significantly larger for the trained monkeys than for the controls, on the trained and untrained side (110 mm² ± 50.3 mm² [p < 0.0001] and 40 mm² ± 22.1 mm² [p < 0.001]). Over half (54%) of the receptive fields sampled extended across more than two glabrous segments of one finger (p < 0.0001 and p < 0.001 for the trained and untrained side, respectively), more than 50% of the RFs covered all of the segments of one digit, and 72% of the hand representation was also mildly degraded on the untrained side (Figure 9).

**Figure 4** (A-D) Compared to the normal representation diagrammed in Figure 1, the topography of the hand was significantly abnormal in the trained monkeys. Area 3b hand zones in two monkeys in which the neurons were driven with receptive fields on the different hand surfaces are represented in Figure 4A-D. Receptive fields commonly extended from the dorsal to the glabrous skin (hatched). Receptive fields at many sites covered the entire glabrous plus dorsal surfaces of at least one finger. Neither of these features is ordinarily recorded in normal monkeys. OM = owl monkey; D = distal, M = middle, P = proximal segments of the fingers; 1-5 = digits; P₁, P₂, P₃, P₄, and P₅ = pads of the palm. Reprinted with permission from Byl N, Merzenich M, Jenkins W. 1996. 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 47:508-520.

**Figure 5** Cortical zones for the two monkeys over which all neurons had multiple receptive field components on more than one digit (hatched), receptive fields that had multiple digits and palmar components (cross-hatched), or receptive fields restricted to a single digit (open areas). OM = owl monkey. Reprinted with permission from Byl N, Merzenich M, Jenkins W. 1996. 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 47:508-520.
dorsal RFs on the trained side included a glabrous representation. Due to the extensive overlap of the receptive fields, it was difficult to accurately measure the size of the cortical representation (Byl et al. 1997).

The second monkey resumed training using a relaxed proximal arm-trunk pulling strategy (keeping the hand on the handpiece and leaning backward/forward or extending/flexing the shoulder to close and release the handpiece). This monkey did not develop signs of motor dysfunction, maintained performance between 10 and 12 trials per minute over 5 months of training, and continued to perform normally on both the target and food retrieval tasks. Electrophysiological mapping indicated that there was only a mild degradation in the hand representation on the contralateral hemisphere of the trained limb, with some overlap of receptive fields across adjacent digits (Figure 7). Only 15% of the cortical penetrations had multiple receptive fields that were discontinuous and recorded from the same penetration, and only 15 of the cortical penetrations had a dorsal receptive field. The size of the cortical area representing the digits was 4.93 mm² (average normal cortical areas range from 3.2 to 5.1 mm² in untrained monkeys) (Stryker et al. 1987).

In both of these monkeys (with and without dystonia), the untrained side showed mild degradation (Figure 8). Although the RFs were smaller than those on the trained side, they were significantly larger than in the controls (p < 0.001; Figure 9), but there were minimal penetrations with multiple RFs and minimal overlaps between adjacent digits or glabrous and dorsal surfaces.

**Figure 6** Percent overlaps for pairs of glabrous receptive fields as a function of distance separating sampled neuronal pairs, for all combinations of all receptive fields in owl monkey (OM) 175. The straight line represents the normal receptive field overlap versus cortical distance function recorded in these monkeys. Reprinted with permission from Byl N, Merzenich M, Jenkins W. 1996. 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 47:508-520.

**Figure 7** Cortical penetration sites and associated receptive fields (RFs) in the primary sensory cortex (area 3b) of the hand for the trained side of the monkey using a hand-squeezing strategy (OM 177). (A, B, C) Receptive fields on the hand for OM 177 and reconstruction of the topographic representations of the hand surface on the somatosensory cortex (area 3b) with penetration sites correlated with the receptive fields on digits E and F, illustrating an abnormal “map” of the hand. The magnitude of area 3b with multiple receptive fields was so extensive that separate drawings were necessary to clearly represent this (illustration A represents the overlap extending from the dorsal to the glabrous surface and illustration B represents the overlap to adjacent digits). (D, E) Outlines of territories over which neurons were driven with receptive fields, larger than normal size, on broad hand surfaces, with abbreviations of the cortical penetration sites matched to the topographical drawing in (C). For this monkey, 54% of the cortical penetrations had multiple receptive fields extending to adjacent digits (A) and 72% of the cortical penetrations including a dorsal receptive field extended to the glabrous surfaces (B). Reprinted with permission from Byl NN, Merzenich MM, Cheung S, Bedenbaugh P, Nagarajan SS, Jenkins WM. 1997. A primate model for studying focal dystonia and repetitive strain injury: Effects on the primary somatosensory cortex. Phys Ther 77:269-284.

**Experiment II**

**Subjects.** Three owl monkeys (*Aotus nancymaeae*)

**Training task.** Actively opening and closing a handpiece (Task B, Experiment I)

**Training paradigm.** The same as for Task B in Experiment I

**Electrophysiological monitoring.** The same as for Experiment I
Results

Two of the three monkeys that performed the active hand-squeezing task developed abnormal hand posturing. One monkey (OM 574) began to use only the third and fourth digits (D3 and D4) to squeeze down on the handle while D1, D2, and D5 hyperextended at the metacarpophalangeal joint and flexed at the interphalangeal joints. The second monkey (OM 311) developed abnormal posturing only of D4.

The topographical map contralateral to the trained limb for OM 574 was degraded, with heavily used digits representing a large topographical area with small RFs (e.g., D3 and D4 occupied an area averaging 42 mm²), while the digits demonstrating a highly abnormal pattern of movement occupied a small topographical area but had large receptive fields (D1, D2, and D5 averaged 100 mm²). These RFs were significantly larger than D3 and D4 and the RFs on the unaffected side (p < 0.001). For OM 311, only the RFs representing D4 showed mixing of hairy and glabrous surfaces and multidigit receptive fields (considered abnormal). However, the receptive field area averaged 18.9 mm² for all of the uninvolved digits and 21.3 mm² for D4 (not significantly different).

The third monkey trained for over a year at the palmar squeezing task and did not develop dystonia. Although this animal performed the task consistently (20 times per minute), he worked in bursts of activity followed by long breaks. The cortical map on this monkey was minimally disorganized, with the mean digital receptive field size significantly larger than that of the controls (16.72 mm²; p < 0.001), but there were no penetrations with multiple receptive fields, nor RFs overlapping adjacent digits or glabrous surfaces and multidigit receptive fields (considered abnormal).
and dorsal surfaces. There was also minimal overlap of the receptive fields as a function of cortical distance.

**Experiment III**

**Subject.** One owl monkey (*Aotus nancymaae*)

**Training task.** This experiment (Blake et al. 2002) involves a case report from an animal involved in a behavioral study unrelated to focal hand dystonia. However, the animal developed dystonic movement patterns while learning to position its hand in a mold that required the first and second digits to contact two motorized tips (Figure 10).

![Figure 10](animal-touches-two-motor-tips.png)

**Figure 10** Apparatus for hand positioning task. The animal contacts the tips of the two probes with the distal phalanges of digits 1 and 2. Contact detectors on the probe tips detect contact, and an LED turns on when contact is established. The animal must hold the hand position for 1 second. In a more advanced version of the task, the animal releases its hand after detecting a temporal pattern of taps delivered by the motors. Reprinted with permission from Blake DT, Byl NN, Cheung S, Bedenbaugh P, Nagarajan S, Lamb M, Merzenich M. 2002. Sensory representation abnormalities that develop dystonic movement patterns while learning to position its hand in a mold that required the first and second digits to contact two motorized tips (Figure 10).

**Training Paradigm**

The animal positioned its right (dominant) hand in the hand mold with the first and second digits on two metal contacts that were each 1 mm in diameter, thus positioning the two digits in an unnatural position (Figure 10). To receive a reward, the animal had to hold the hand in place for several hundred milliseconds before releasing. With D1 and D2 in position, a series of 100- to 200-μm taps (creating minimal indentations in the skin) were delivered to the fingertips.

This task, a cross-digit interval discrimination task, was part of a planned series of experiments documenting changes related to sensory discrimination. The task used a limited hold reaction time paradigm, as the trial began with an orienting response to facilitate hand placement. Once the animal learned placing, the stimuli began. In all cases, each element of the series was a pair of taps separated by an interval. In the pair of taps, a tap to the index finger occurred before a tap on the thumb. Then a new pair of taps occurred after a 500-millisecond interval. After at least two standard interval tap pairs, the tap interval length changed to 250 milliseconds and then to 100 milliseconds. The animal was rewarded with Tang for releasing after the shortened interval length, and time-outs followed releases at other times. After 2 months of training, accuracy dropped below 50% of the starting performance.

**Electrophysiological Monitoring**

Electrophysiological monitoring was the same as for Experiment I. In addition, shortly before the full focal hand dystonia developed in the right hand, a chronic electrode with a dense array of 49 high-impedance parylene-iridium microelectrodes was implanted in a 2 x 2 mm cortical area in the 3b hand area. deCharms and colleagues (1999) have described the techniques for implantation.

**Data Analysis**

This was a single-case, post-test design that emphasized descriptive differences between baseline and post-training performance and differences from normative controls. The Student's t-test was used to compare mean differences of receptive field size between the controls (Stryker et al. 1987) and the trained monkeys. The remaining data were presented descriptively. Change in motor performance was correlated with change in neurophysiological recordings.

**Results**

Within a few weeks of training at the task, the animal developed a tremor while trying to place the digits on the targets. The number of trials per minute decreased from 19 to 9 after 7 weeks of training, and the percent performed correctly dropped to 16%. The tremor began as the hand approached the target, with the animal often pulling the hand back with the other hand. This condition worsened over 4 months and then digits 3, 4, and 5 assumed an abnormal posture (extension of the metacarpophalangeal joints and flexion at the interphalangeal joints).

In the fifth month, daily receptive field mapping was initiated with the implanted stationary electrode array. D1 and D2 were monitored. Motor dysfunction continued to deteriorate over the next 2 months. The size of the RFs increased from 30 to 101 mm² on the affected digits (significantly larger than those of normal controls; p < 0.0001) and mixing of responses became prominent with receptive fields overlapping across both digits (Figure 11). Hairy-glabrous, multiple-digit, and hand-face mixing of RFs was observed in responses on single electrodes.

In addition, cortical substitutions began to occur. The border between the hand and the face became patchy, with islands of face activity progressively invading the digital representations. The medial face expanded into the hand representation. This area of the face was consistent with a cortical columnar substitution (Figure 12). Again, there was overlap of adjacent digits across the cortex in the trained
monkeys, with the RF overlap documented up to a cortical distance of 1,800 microns (Figure 13). Across the same period, adjacent electrodes often maintained the same receptive fields. The thalamus was also mapped in this animal, and receptive field sizes and mixing were also found to be abnormal, although not as abnormal as those in the cortex.

Rat Model: Repetitive Strain Injury/Focal Hand Dystonia

Objective. The objective of these experiments (Barbe et al. 2003, 2005; Barr and Barbe 2002, 2004; Barr et al. 2004; Clark et al. 2003, 2004) was to investigate the immunohistochemistry of the soft tissues of the upper limb and motor performance of the upper limb after attended, repetitive, voluntary forelimb reaching and food grasping.

Subjects. Fifty-seven adult female Sprague-Dawley rats (age 12 to 14 weeks), with random assignment to group

Training task. The rats were trained to reach for, grasp, and retrieve food pellets from a cylinder.

Training Paradigm

The rats were first shaped to perform the task and then trained 3 times per week at the task. The trained animals were food deprived, with body weight maintained at 80-90%. The rats were placed in operant test chambers after shaping. A tube 1.5 cm long was positioned at shoulder height, at a distance that required the rat to fully extend the elbow to reach the pellet (45 mg), which was dispensed every 15 or 30 seconds (depending on whether it was the low- or high-rate experiment). An auditory indicator signaled the delivery of the pellet. The rats trained 3 days a week for 3 to 8 weeks with the daily task divided into four half-hour training sessions separated by 1.5 hours. This kept the reach frequency high during each training period. A reach was defined as a trial where the rat reached the forepaw beyond a line drawn 0.5 cm in the tube.

Four training regimes were studied. Each regime used 45-mg pellets and included training for 2 hours a day 3 days a week. The first regime was based on a low rate and a low force (LRLF): the target rate was 2 to 4 reaches per minute at low force. Food pellets (45 mg) were delivered during the
training period. The second regime was high rate, low force (HRLF), with a target rate of a minimum of 4 reaches per minute. The third paradigm—low rate, high force (LRHF)—called for 2 to 4 reaches per minute and a target force of 50% to 70% maximum grip force. For the fourth paradigm, high rate and high force (HRHF), the reach rate was a minimum of 4 per minute at 50% to 70% maximum grip force.

The researchers monitored the reaching rate and videotaped movements, and noted two distinct reaching and grasping patterns: scooping (the animal placed a semi-open forepaw over the food pellet and then dragged the pellet along the tube and scooped it into the mouth); and raking (this was an inefficient extreme of scooping, in which the animal made repeated, unsuccessful attempts to contact the food pellet by moving the paw back and forth like a rake to bring the pellet to the mouth).

The number of minutes the rat participated in the task was monitored. Both low and high frequency rates were studied. The animals were sacrificed after 5 weeks of training to assess the tissue response at different durations of training. The animals were euthanized at weekly endpoints using Nembutal (120 mg/kg body weight). The researchers examined the levels of serum IL-1α and IL-1β (3 to 8 samples per group) from each group of animals and collected blood samples from the heart, which were centrifuged and serum aspirated. Total protein was determined using BCA-200 protein assay kits.

**Research Design**

These experiments are consistent with a controlled research design with random assignment to (1) controls (no shaping), (2) shaping (task performance), and (3) shaping plus training (rest and shaping). Gross movement patterns were noted and recorded as present (>1 per minute) or absent (<1 per minute). Cytokines (IL-1α and IL-1β), inflammatory cells, and macrophages (including infiltrating macrophages [ED1] and resident tissue macrophages [ED2]) were described as part of the inflammatory and degenerative process. The tissues from the contralateral, nonreach limb and hindlimb were also examined. Cortical mapping studies are in process.

**Data Analysis**

The investigators studied differences between high- and low-repetition groups by applying an analysis of variance (ANOVA; p < 0.05). They analyzed differences in reach rate, task duration, and numbers of macrophages by week and by tissue, using a combination of ANOVA (p < 0.05) and, for post hoc analyses, the Bonferroni method for multiple comparisons (p < 0.0167). Reach rate and task duration were also analyzed by week. Movement patterns and ED1-1R and ED2-1R macrophages were analyzed over weeks of task performance using an ANOVA (p < 0.05) without interactions followed by post hoc analysis (p < 0.0167). An ANOVA (p < 0.05) was also applied to study the differences between the rats that reached at low versus high rates.

**Results**

The self-initiated mean reach rate was highest at the beginning of the training, 8.27 reaches per minute (±.66 standard error of measurement, or SEM), with a significant decrease in reach rate by the end of week 5 (6.82, ±.66 SEM reaches per minute, p < 0.0028) and week 6 (6.12 reaches per minute, ±.52 SEM; p < 0.0070). For the low-repetition group, there was no significant difference in reach rate across weeks (p < 0.140), with a mean rate of 3.0i reaches per minute at 50% to 70% maximum grip force.

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Cytokine changes in serum levels of IL-1α were measured in the high-repetition group (increased 27%) with no significant changes in IL-1β. In the low-rate group, there were no significant changes in IL-1α or IL-1β, although at
8 weeks there was a trend toward a decrease in IL-1α in the low-rate group. These findings suggest a dose response relationship between reach rate and physiological responses, with the higher reach rate associated with signs of inflammation (e.g., IL-1α).

Both reaching groups showed a decrease in motor performance and histological changes associated with tissue injury, observed as a rise in cellular and tissue responses characteristic of inflammation. Exposure and dose-dependent increases were measured in phagocytic macrophages (HRHF > HRLF > LRLF). Degraded myelin was present, indicating myelin breakdown. The researchers noted an increase in intraneural inflammatory cytokines and fibrotic nodules around the median nerve at the wrist. They also documented signs of nerve tethering and a decrease in nerve conduction in the span of the nerve across the carpal tunnel (Clark et al. 2003, 2004). Sensory changes also occurred as the number of weeks of HRHF task performance increased.

In the HRHF group, reach rate decreased after week 5 as did task performance time. This was followed by the emergence of a clumsy, raking movement pattern instead of scooping. The animals could no longer close the digits to lift the food pellets. This change in motor skills was hypothesized to represent compensation for tissue injury (e.g., inflammation). The researchers also observed discrete sites of disruption in tendon fibers and infiltration of phagocytic macrophages. The number of macrophages remained high at 8 weeks, but there was some rebound in the reach rate (e.g., possibly due to regeneration and healing). However, the motor performance did not return to normal.

Cortical mapping has begun on these animals. Preliminary data analysis reveals signs of topographical degradation of both the sensory and motor cortices. These findings are being studied more thoroughly.

Integration of Findings from Animal Studies of Focal Dystonia

The results of these animal studies support a relationship between motor control and sensory processing. There were abnormalities in receptive field sizes, cortical column sizes differentiating different digits, and a mixing of normally segregated response modalities. In animals with movement dysfunction that simulated focal hand dystonia, receptive fields at single sites in the primary somatosensory map increased up to 10 times normal size, with sensory physiology abnormalities largest on the digits most affected. Response modalities, such as single digit representations or representations of glabrous or hairy skin, became mixed in the hand maps of animals with the disorder. Cortical columns leading to the adjacent digit (e.g., Figure 13) were up to four times the normal size.

As a result of the abnormality in cortical column size, the capacity of the somatosensory system to represent independent inputs was reduced dramatically. If the hand map is normally 6 mm² and each cortical column is 0.25 mm², then there are roughly 24 independent sensory modules representing the hand. If instead the column size is 4 mm², as seen in the animals with FHD, there can be only one or two independent modules representing sensory inputs across the hand. This reduction in the dimensionality of the input would be expected to have a detrimental effect on sensorimotor processing; rather than independent action of each digit, there would be a mixing of inputs to different digits (Figure 14). The findings reported here need confirmation through additional research.

The cortical column abnormality and enlarged receptive fields were also observed in the somatosensory cortex in the hemisphere contralateral to the untrained limb. In human subjects, focal dystonia can develop in both limbs. The hypothesis is that this occurs because of genetic risk factors, but it is also possible that bilateral hand dystonia may result from the spread of somatotopic degradation. Additional research regarding the unusual somatosensory topography in patients with focal hand dystonia must also include analysis of neurophysiological mechanisms responsible for controlling excitation and inhibition.

Maps of somatosensory cortical maps in nonhuman primates suggest that modular independence occurs on a spatial scale of about 0.5 mm in normal animals. These maps are plastic and can adapt to attended, repetitive behaviors that are rewarded, spaced, and progressive in difficulty (Buonomano and Merzenich 1998; Kleim et al. 1998, 2006; Nudo et al. 1996b; Xerri et al. 1999; Wang et al. 1995). Attended sensory inputs that occur near simultaneously may become co-represented (Wang et al. 1995). A violation of
modular separation in sensory cortex from behaviorally driven cortical plasticity may lead to a cascade of motor control problems.

Discussion

The two animal models of repetitive strain injury–induced FHd described in this article provide evidence that attended, precise, repetitive, and near simultaneous movements (e.g., end-range motions of adjacent fingers or rapid reversal of agonists and antagonists) can disrupt normal control of movement at a target task. These movements do not have to be forceful; they only have to challenge the limits of the time required for independent neural registration. The primate models described above suggest that one of the potential etiologies of focal hand dystonia could be high levels of repetitive, alternating or near simultaneous movements of adjacent digits. If these movements seriously degrade topographical representations, then motor control could be compromised.

But etiological studies in both animals and humans suggest that focal hand dystonia may also result from neurophysiological, environmental, and behavioral risk factors. The ultimate presentation of the signs and symptoms of focal dystonia (phenotype) may result from an interaction and culmination of multiple factors such as the following:

- genetics (Gasser et al. 1996; Illarioshkin et al. 1988; Leube et al. 1996; Ozelius et al. 1997);
- an imbalance of inhibitory and excitatory pathways in the globus pallidus or substantia nigra (Black et al. 1998; DeLong 1990; DeLong et al. 1985; Perlmutter et al. 1997);
- cortical dysfunction (Chase et al. 1988; Defendini and Fahn 1988; Deuschl et al. 1995; Gilman et al. 1988; Tempel and Perlmutter 1993; Toro et al. 2000);
- degradation of somatotopic representations in the thalamus (Lenz and Byl 1999; Uitti et al. 1995; Zirh et al. 1998);
- disruption of sensory perception, somatosensory representation, and/or cortical sensory activation (Bara-Jimenez et al. 1998, 2000; Butterworth et al. 2003; Byl and Topp 1998; Byl et al. 1996a,b,c, 1997, 2000a,b,c, 2002; Chen and Hallett 1998; Elbert 1998; McKenzie et al. 2003; Tinazzi et al. 1999, 2003);
- abnormal presynaptic desynchronization of movement or abnormal muscle spindle afferent firing (Grunewald et al. 1997; Toro et al. 2000);
- abnormal gating of somatosensory inputs (Murase et al. 2000);
- disruption of inhibition in the spinal cord (Chen et al. 1995; Kaji et al. 1995; Nakashima et al. 1989; Naumann and Reiners 1997; Panizza et al. 1989, 1990);
- modifications in anatomical structures (Topp and Byl 1999; Wilson et al. 1991);
- personality characteristics of perfection and perseverance (Altenmuller 2003; Jabusch et al. 2002);
- stressful jobs that require high levels of repetitive hand use (Bara-Jimenez et al. 1998; Barbe et al. 2003; Barr and Barbe 2002; Byl 2004; Byl et al. 1996c, 1997, 2000a,b,c, 2002; Candia et al. 1999, 2002; Chen and Hallett 1998; Elbert et al. 1998; Fry 1986; Ikeda et al. 1999; McKenzie et al. 2003; Odergren et al. 1996; Sanger and Merzenich 2000; Sanger et al. 2001; Tinazzi et al. 2003; Topp and Byl 1999);

How each of these factors is weighted to predict focal dystonia has yet to be determined.

In terms of treatment, the animal studies reported here suggest that preliminary signs of stress (e.g., a temporary reduction in task performance) may indicate that the intense repetition of a task could be a risk factor for the development of involuntary dystonic movements. For example, in the primate studies, the primates temporarily stopped performing the task after 2 to 3 weeks. Barbe and colleagues (2003, 2005) reported an early, temporary decline in frequency and quality of repetitive movements. In both models, these signs appeared before the observation of motor dysfunction. In the rat model, after 8 weeks of high force or high rate of repetitive hand use, 100% of the rats shifted from a coordinated scooping strategy to a clumsy raking strategy. In the primates, after the initial slowing of practice intensity, the animals either resumed or modified their strategy. Those that modified their behavior did not develop movement dysfunction. Further, by the time motor dysfunction occurred in the monkeys that reduced the intensity of their practice, there were no longer signs of acute inflammation (Topp and Byl 1999). Early tissue sampling during the animal’s period of hesitation to perform the task might have revealed signs of inflammation in the tendons and nerves. However, central cortical changes were noted after the development of abnormal motor performance, and these changes were consistent with negative learning.

Interestingly, the findings from human FHd studies are strikingly similar to those from the animal studies described in this article. In both animal and human studies, there are signs of cortical degradation not only on the affected (trained side) but also on the unaffected side. Electrophysiological studies in animals have documented a reduction in the area of the somatosensory hand representation, excessively large receptive fields overlapping adjacent digits, and dorsal and glabrous surfaces with receptive fields that persist across broad columnar distances (Blake et al. 2002; Byl et al. 1996c, 1997). There are also reports of long thalamic trajectories on the trained side of monkeys with FHd (Blake et al. 2002). In human studies of patients with hand dystonia, digits one through five were no longer sequenced from...
inferior to superior but were located in the same place ("clumped") (Bara-Jimenez et al. 2000; Byl et al. 1996a,b,c, 1997; Chen and Hallett 1998). In addition, in patients with general dystonia, long trajectories extending beyond the usual differentiation between individual digits have appeared in the thalamus (Lenz and Byl 1999). In fMRI stud-
ies of patients with focal hand dystonia, there have been reports of excessive activation in some cortical areas (Chase et al. 1988; Defendini and Fahn 1988; Deuschl et al. 1995; Gilman et al. 1988; Pujol et al. 2000; Tempel and Perlmutter 1993), abnormal gating of somatosensory inputs (Murase et al. 2000), abnormal presynaptic desynchronization (Torro et al. 2000), and imbalance of inhibitory and excitatory pathways in the globus pallidus or substantia nigra (Black et al. 1998; DeLong 1990; DeLong et al. 1985; Perlmutter et al. 1997).

Some researchers interpret the bilateral findings as supportive of a genetic hypothesis rather than a behavioral hypo-
thesis, as reported in the primate studies. Interestingly, in patients who have a gene for cervical torticollis, all patients
with the gene do not necessarily develop the dystonia (Gasser et al. 1996; Illarioshkin et al. 1988; Leube et al. 1996; Ozelius et al. 1997), and all patients with cervical dystonia do not necessarily have a gene for cervical torti-
collis.

It is important to note that, in the behavioral animal studies reported in this review, not all of the animals
that were trained at a repetitive task developed a hand dystonia. In the rat studies, if the rate of repetition and the
force were low, the animals did not necessarily degrade their motor performance. In the primate studies, the animals
who did not develop a movement problem performed the task slowly, took frequent breaks, required long training
periods (45 to 90 minutes to perform a limited number of repetitions at the target task), performed the task several
times a day for shorter training periods (30 minutes 3 times a day instead of 1.5 hours once a day), or did not use
a strategy involving near simultaneous movements (e.g., they employed a large-strategy trunk and arm movement
instead of a hand movement). Consequently, the criteria of near simultaneous, coincident inputs to the skin were not
met.

Clinically, not all individuals who perform rapid, repeti-
tive, alternating digital movements develop a repetitive
strain injury or a focal hand dystonia. For example, some
musicians learn to reduce stress by using performance strat-
egies that include moving from the shoulder and elbow while minimizing recruitment of extrinsic finger flexor and
extensor muscles of the hands. These movement strategies,
coupled with the recruitment of endurance-based intrinsic
hand muscles (e.g., phase I fibers of the lumbricals and
interossei), can help maintain the optimum functional posi-
tion of the hand, maintain the optimal length of hand
muscles, and minimize co-contractions of adjacent digits
with shared tendons. Releasing the pressure down rather than lifting the fingers up can also passively unweight
the force down without requiring active extension. These strat-
egies are based on healthy kinematics and may prevent the
development of focal dystonia of the hand if implemented
early as a correct strategy for performing artists.

Interestingly, there may also be personality factors that
put individuals at risk to develop a hand dystonia, as became
evident in the primate studies. Some primates were driven to
perform tasks quickly with a lot of force whereas others
performed the tasks slowly, took a lot of breaks, or used a
trunk strategy rather than a hand-squeezing strategy. In hu-
man studies, musicians with FHd were more likely to have
a history of anxiety, perfectionism, perseveration, and pho-
bias compared to musicians without hand dystonia (Jabusch
et al. 2002).

Anatomical variants may introduce another set of risk
factors for the development of focal dystonia. For example,
one of the owl monkeys in the experiments described above
had a congenital defect of the flexor profundus and subli-
mus tendons on D4 on the trained side and D3 on the un-
trained side. This primate developed signs of dystonic
movement of D4 after only 5 weeks of training. This is
consistent with research reports of human studies. As com-
pared with healthy controls, individuals with FHd tend to
have greater restrictions in finger spread (Leijnse 1997;
Wilson et al. 1991), forearm rotation, and shoulder rotation
(Byl et al. 2002; McKenzie et al. 2003; Wilson et al. 1993).
In one study, those with severe FHd had more restrictions
in clinical musculoskeletal performance parameters than those
with mild FHd (Byl et al. 2002). There were also differences
in fine motor performance and sensory discrimination in
patients with severe versus mild hand dystonia (Byl et al.
2002; McKenzie et al 2003; Sanger et al. 2000; Tinazzi et
al. 2003).

One question that needs to be answered is whether ab-
normal pallidal discharge is correlated with the develop-
ment of FHd after repetitive hand squeezing. If so, another
question would be whether surgical inactivation of the glo-
bus pallidus internus would restore hand control. To try and
answer this question, macaque monkeys were trained fol-
lowing a paradigm of hand squeezing where both the fre-
quency and the difficulty of the task could be increased.
Unfortunately, when the force of the grip was increased to
create stressful effort, the monkey was not able to perform
the task without breaking down the integrity of the skin on
the palm of the hand. Thus, it was impossible to drive suf-
cient demanding repetitive, stressful alternating move-
ments to degrade the topographical representation of the
hand and/or degrade motor control.

Limitations of an Animal Model for Studying Focal Dystonia

While there are many advantages of using behavioral ani-
mal models for studying focal dystonia, particularly in
terms of understanding the neural basis of dystonia, there
are also limitations. In nonhuman animal studies, it is dif-
cult to obtain feedback about pain, depression, or anxiety.
Therefore, the deterioration of motor performance calls for careful observation to determine whether the movement dysfunction results from pain or from loss of control. In the studies reported here, early changes in performance may have been due to local tissue trauma. But because the motor control problems developed slowly over time, it was presumed that the motor dysfunction was due to central cortical changes rather than peripheral pain. In nonhuman primates it is also difficult to document nontask-related sensory abilities such as specific sensory discrimination skills (e.g., graphesthesia, kinesthesia, stereognosis) and fine motor, rapid alternating movements.

Another disadvantage of the animal models reviewed here is that both motor and sensory electrophysiological mapping cannot easily be carried out in the same session. Sensory mapping takes place under Pentabarb-induced anesthesia, and motor mapping under Ketamine-induced anesthesia. It is difficult to change these drugs during the electrophysiological testing period.

In addition, careful control of the number of animals (especially nonhuman primates) approved for research limits the opportunity for weekly or initial-symptom onset as times for sacrifice. This limitation compromises the ability to assess simultaneous peripheral and central changes. While there are good animal models for environmental enrichment and plasticity, it is difficult to create animal models with the carefully controlled, attended, repetitive, progressive learning-based paradigms necessary to restore high-level cognitive and motor performance. Furthermore, if there is an impairment in the executive function of the frontoparietal pathways that are required to integrate sensory and motor cortices in patients with FHd, then the question is whether animal studies can sufficiently isolate and measure complex functions in each of these pathways to facilitate more effective remediation strategies for dystonia.

An animal model of dystonia not detailed in this article concerns the genetic mutation associated with generalized dystonia and torsion dystonia, the DYT1 gene, which is an autosomal gene of low penetrance. Positron emission tomography has revealed increased glucose metabolism in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area, a metabolic change that can interfere with the analysis of sensory information and explicit motor learning. These brain regions have high levels of Torsin A and Torsin B (Augood et al. 1999). Animal models of spastic torticollis have provided insight on the relationship of dysfunction in different brain regions and abnormal head postures. Animal models of blepharospasm have documented hyperactivity in a variety of brain regions (frontal cortex, striatum, thalamus, and cerebellum). Experiments have focused on the effects of modified levels of dopamine on excitability—depleting dopamine increases excitability and increasing it decreases excitability (Wichmann and DeLong 2000).

It appears that blurring sensory and motor modules that are normally separated may be one key component of focal hand dystonia. This finding suggests that independent sensory and motor training would be the most efficacious route to reestablish normal function. Such behavioral training would need to result in the normalization of motor modular independence, sensory modular separation, and motor function. Animal models of forced use paradigms have been described for post-stroke rehabilitation (Nudo et al. 2000), but it is not clear these paradigms would be sufficient to restore somatosensory representation and fine motor control in an animal with focal hand dystonia. It may be equally challenging to use a primate animal model to test the effectiveness of sensory motor retuning, in which splinting controls some digits while others are involved in motor behavioral training (Candia et al. 2002) or in sensory training using Braille (Zeuner et al. 2002; Zeuner and Hallett 2003). In nonhuman primate models, it may also be difficult to evaluate the effectiveness of other attended, progressive, repetitive training paradigms such as learning-based sensorimotor training (Byl and McKenzie 2000; Byl et al. 2004). Thus, today, with an increase in the incidence of focal hand dystonia and improvements in imaging techniques, more studies are using noninvasive functional magnetic resonance imaging, magnetoencephalography, and magnetic stimulation to study the neurophysiological basis as well as the treatment effects of focal dystonia using human models (Hallett 2006).

Confirmation of Sensory Processing Deficits in Humans with FHd

With the documentation of sensory map abnormalities in the animal model, it was predicted that disruption in sensory processing measures would be measured in patients with focal hand dystonia. One study (Byl et al. 1996a) reported abnormalities in graphesthesia and manual form perception in patients with focal hand dystonia, two percepts that require integration of somatosensory input across the skin. In two other clinical studies of patients with hand dystonia, the researchers reported poor spatial acuity on the fingertips (Bara-Jimenez et al. 2000; Sanger et al. 2001) as assessed with a grating orientation task (Johnson and Phillips 1981). Spatial localization was also abnormal in patients with focal hand dystonia (Bara-Jimenez et al. 2000). Other studies reported abnormal temporal discrimination in patients with writer’s cramp (Sanger et al. 2001) and in patients with hand dystonia (Tinazzi et al. 1999).

fMRI-based studies report area 1 distances from digit two to digit five as abnormally small and disordered in patients with focal hand dystonia (Butterworth et al. 2003). Researchers using magnetic source imaging in patients with focal hand dystonia have also reported temporally abnormal evoked magnetic fields and abnormal spatial organization (Bara-Jimenez et al. 1998; Byl et al. 2000a, 2002; McKenzie et al. 2003). These findings are consistent with the electrophysiological findings in the nonhuman primate studies.
Conclusions

The owl monkey model of focal hand dystonia and the rat model of repetitive strain injury have reported an array of neurophysiological abnormalities after training. Enlarged receptive fields, enlarged cortical columns, and a breakdown of modality separation are all now known to be part of the physiological manifestation of dystonia. Sensory testing in humans reveals a parallel set of psychophysical and physiological abnormalities associated with the disorder. Thus, the etiology of focal hand dystonia is considered multifactorial. Treatment strategies based in part or in whole on restoring cortical sensory and motor topography hold promise for restoring motor control in patients with focal hand dystonia. As this work progresses, combined animal and human studies should serve to increase understanding of the neural basis of focal dystonia and more effectively guide interventions.

References


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