Invited Review

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HIGHLIGHTED TOPIC | *Neural Changes Associated with Training*

Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord

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Adkins, DeAnna L., Jeffery Boychuk, Michael S. Remple, and Jeffrey A. Kleim. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. *J Appl Physiol* 101: 1776–1782, 2006. First published September 7, 2006; doi:10.1152/japplphysiol.00515.2006.—The motor cortex and spinal cord possess the remarkable ability to alter structure and function in response to differential motor training. Here we review the evidence that the corticospinal system is not only plastic but that the nature and locus of this plasticity is dictated by the specifics of the motor experience. Skill training induces synaptogenesis, synaptic potentiation, and reorganization of movement representations within motor cortex. Endurance training induces angiogenesis in motor cortex, but it does not alter motor map organization or synapse number. Strength training alters spinal motoneuron excitability and induces synaptogenesis within spinal cord, but it does not alter motor map organization. All three training experiences induce changes in spinal reflexes that are dependent on the specific behavioral demands of the task. These results demonstrate that the acquisition of skilled movement induces a reorganization of neural circuitry within motor cortex that supports the production and refinement of skilled movement sequences. We present data that suggest increases in strength may be mediated by an increased capacity for activation and/or recruitment of spinal motoneurons while the increased metabolic demands associated with endurance training induce cortical angiogenesis. Together these results show the robust pattern of anatomic and physiological plasticity that occurs within the corticospinal system in response to differential motor experience. The consequences of such distributed, experience-specific plasticity for the encoding of motor experience by the motor system are discussed.

skill training; endurance training; strength training; motor cortex plasticity; spinal cord plasticity

ADULT MOTOR BEHAVIOR IS HIGHLY adaptive and can be modified in response to a variety of different motor experiences, including skill, strength, and endurance training. Acquired motor behaviors also endure in the absence of continued training, demonstrating that motor experience is somehow persistently encoded within the nervous system. There is now extensive evidence that motor training can induce structural and functional adaptation ("plasticity") within several motor areas, including basal ganglia (13, 21, 39), cerebellum (14, 47, 48), and red nucleus (27). The present review focuses on plasticity within motor cortex and spinal cord that occurs in response to skill, exercise, and endurance training.

Virtually all acquired motor behaviors contain some element of skill learning, increased strength, and increased endurance that develop through extensive practice. We will distinguish between these different classes of motor behaviors on the basis of the primary behavioral demand imposed by the training experience. Skill training is defined as the acquisition and subsequent refinement of novel combinations of movement sequences. Strength training is defined as resistance exercise resulting in an increase in force capacity, and endurance training refers to exercises that increase the capacity for continued motor output. Evidence is reviewed that these three different motor training experiences are encoded though disparate forms of anatomic and neurophysiological changes across the motor cortex and spinal cord.

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MOTOR CORTEX

Skill training. Primary motor cortex is organized into highly interconnected neural assemblies (localized groups of neurons with similar inputs and outputs) that control discrete movements across different joints (i.e., hand, finger, legs) (16, 38, 72). The coordinated activation of these assemblies then encodes complex, multijoint movements such as reaching (22). It has been proposed that the acquisition and refinement of novel movement sequences during skill learning involve changes in

the connectivity between these neural assemblies (55). These changes are reflected as alterations in cortical synapse number, synaptic strength, and the topography of stimulation-evoked movement representations.

Adult rats trained on a complex visuomotor task that requires the animals to learn limb placement and posture control to traverse a complex obstacle course ("acrobatic task") show increases in synapse number within motor cortex compared with control animals that walked an unobstructed course (35, 36, 46). Similarly, skilled reach training increases the complexity and density of forelimb motor cortical dendritic processes (3, 5, 23, 81) and synapses per neuron (40, 45). The increase in synapse number is consistent with enhanced postsynaptic potentials within the hemisphere contralateral to the trained paw (30, 56, 70).

These synaptic changes are thought to represent changes in cortical circuitry resulting in a reorganization of the neural assemblies encoding movement. In support of this notion, reach-trained rats show an expansion of microstimulation-evoked movement representations within motor cortex (motor maps) corresponding to the specific motor region that controls the muscle groups used in the task. The specificity of the training induced cortical reorganization was demonstrated in squirrel monkeys initially trained on a skilled digit manipulation task that induced only an expansion of digit representations in motor cortex (60). Cessation of skilled digit training followed by training on a skilled wrist manipulation task reduced the previously enlarged digit representational map while also expanding the wrist motor map in the same animals (60). Skilled reach-trained rats also exhibit an expansion of distal (wrist and digit), but not shoulder and elbow, movement representations in the motor cortex compared with controls (41). Furthermore, this learning induces synaptogenesis that is colocalized to regions in motor cortex exhibiting the expansion of wrist and digit cortical map reorganization (40). The reorganization of motor maps is not simply due to increased forelimb use, as demonstrated by the lack of distal forelimb motor map expansion in rats trained to repetitively press a lever (41), continuously reach for an unattainable pellet (45), or run in running wheel (44). Similarly, squirrel monkeys trained to retrieve food pellets from a large well that does not require the development of novel skilled digit movements do not show any change in digit movement representations despite having produced ~13,000 digit flexions during the course of training (68). These data indicate that training on a novel skill produces alteration in the neural circuitry in the motor cortex that are specific to the muscle groups necessary for execution of the trained task and do not occur following simple repetitive use of those same muscle groups.

Transcranial magnetic stimulation (TMS) and neuroimaging techniques have been used to demonstrate similar changes in human motor cortex (12, 32, 37, 65). Subjects trained to produce skilled digit movements on a piano show an increase in the area of digit representation corresponding to the trained hand and a decrease in motor-evoked potential (MEP) threshold (64). These changes do not occur in the contralateral, nonplaying hand or in control subjects. Training subjects on skilled ankle (67) or tongue (74) tasks also increases movement representation area and MEP amplitude compared with untrained controls. Cross-sectional studies have revealed comparable changes among individuals with varying degrees of motor skill. For example, highly skilled racket players have larger hand motor representation and enhanced MEP amplitudes compared with less proficient players and nonplaying controls (66). Similarly, blind braille readers have larger cortical representation of the braille-reading digit compared with the contralateral digit or nonbraille readers (62, 63, 65). Tyc et al. (76) report that highly skilled volleyball players have significantly larger and more overlapping representations of medial deltoid and carpi radialis muscles than runners. This is consistent with the fact that volleyball players have acquired coordinated shoulder movement sequences, whereas runners do not. Thus the specific nature of the reorganization is dependent on the specific behavioral demands of the training experience.

The cellular mechanisms of learning-dependent motor cortex plasticity are also being revealed. For example, skilled motor performance, motor map reorganization, and synapse number are all dependent on constitutive protein synthesis within motor cortex (42). Although the specific proteins required for such plasticity are yet to be identified, brain-derived neurotrophic factor (BDNF) appears to be involved. Inhibition of BDNF by injection of antisense oligodeoxynucleotides (42), receptor antagonists or BDNF receptor antibodies (78) in rat motor cortex disrupts motor reorganization and impairs performance of motor skill (78). Kleim et al. (43) showed that human subjects with single-nucleotide polymorphism substitution (Val66Met) in the BDNF gene exhibit reduced motor map reorganization and corticospinal excitability following training on several fine motor tasks compared with subjects without the BDNF polymorphism.

Taken together, experimental data demonstrate that increases in protein synthesis, synaptogenesis, and map reorganization within motor cortex represent a set of coordinated neuronal changes that drive the acquisition and performance of skilled movement (Fig. 1).

Strength training. Although strength training induces well-characterized intramuscular adaptations, growth of muscle fibers cannot account for all observed increases in strength. For example, significant strength gains occur before muscle hypertrophy (2, 28, 34, 51), and significant loss of strength from either disuse (17) or detraining (24, 58) precedes muscle atrophy. Furthermore, increases in muscle strength on one task do not necessarily transfer to other tasks using the same muscle (19, 26, 29, 52). Finally, unilateral training increases strength in the corresponding contralateral muscle (cross-education) (18, 25, 31, 57, 84). Together, these data suggest that the central nervous system must also contribute to training-dependent increases in strength. However, it is unclear whether and to what extent strength training induces predominately cortical vs. spinal cord plasticity. Comparing TMS- and transcranial electrical stimulation (TES)-evoked MEPs can provide a means of separating out activity-dependent changes that are either predominately cortical or corticospinal. TMS primarily activates corticospinal neurons via indirect activation of transynaptic cortical neurons and TES stimulates the corticospinal tract monosynaptically (15). For example, TMS and TES MEPs in the first dorsal interosseous muscle at rest do not differ after 4 wk of strength training (9). However, the slope of the relationship between (TMS or TES) MEP amplitude and torque was smaller during submaximal contractions suggesting plasticity within spinal cord circuits. Furthermore, skill training

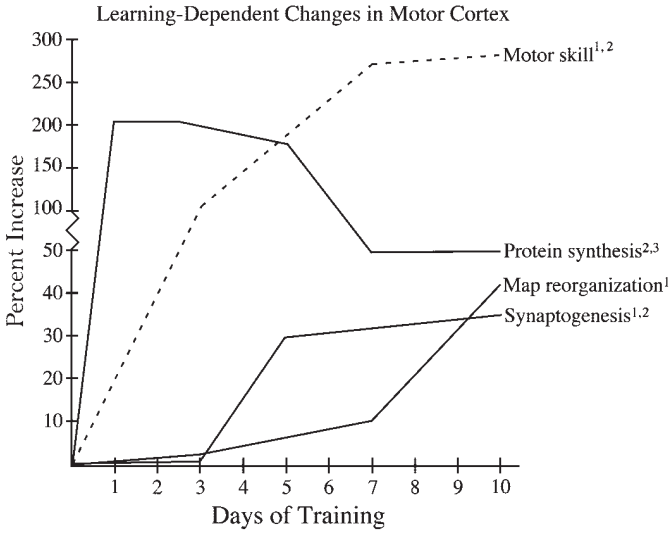

Fig. 1. Time course of molecular, anatomic, and physiological plasticity within rat motor cortex during motor skill reach training. Measures are expressed as percent increase from control or pretraining levels. Motor skill level increases rapidly over the first few days of skill training [[1]Kleim et al. (46); [2]Kleim et al. (45)]. The early phase of skill learning is characterized by an increase in the synthesis of various proteins, including the immediate early gene c-*fos* [[1]Kleim et al. (46)] and the cAMP response element binding protein ([3]J. A. Kleim, P. M. VandenBerg, C. Cole, and N. Thomas, unpublished observations). Later phases of skill training are accompanied by significant increases in synapse number [[1]Kleim et al. (46); [2]Kleim et al. (45)] and motor map reorganization [[2]Kleim et al. (45)].

on a visuomotor training task that requires participants to trace the vertical component of computer-generated figures induces an increase in TMS-evoked maximum motor-evoked response (of resting muscles) along with a significant decrease in MEP threshold, whereas conversely, strength training reduces the maximum motor evoked response and the slope of the stimulus-response interaction (33). In addition, Carroll et al. (9) and Jensen et al. (33) found that strength-trained individuals display lower TMS-evoked MEPs relative to untrained controls, suggesting a training induced decrease in corticospinal excitability.

To further examine how strength vs. skill training influences the motor cortex, Remple et al. (69) trained rats on a reaching task with different behavioral demands. The first task required the acquisition of skilled reaching movements to target and retrieve a food reward. The second task also required the same skilled movement pattern but additionally required the animals to develop increased forelimb strength to obtain the reward (Fig. 2). Rats trained on both tasks showed expansion of wrist and digit representations compared with nonreaching controls. Thus, despite the task requiring increases in elbow, shoulder, wrist, and digit strength, strength-trained animals only showed an increase in wrist and digit representations comparable to those of the reaching controls. If strength training did influence movement representations, then it is expected that there would be increases in all four motor representations. Thus, unlike skill training, strength training does not appear to induce reorganization of movement representations.

Endurance training. In motor cortex, the primary effect of endurance training is on cerebrovasculature. Exercise induces angiogenesis and increases blood flow, presumably to meet the increased metabolic demands of cortical neurons. Swain et al. (75) reported that animals given free access to a running wheel for 30 days had increased blood flow and greater angiogenesis in the motor cortex compared with sedentary rats. Exercise-induced changes in blood flow and angiogenesis were specific to the motor cortex and were not found in the frontal cortex or other subcortical areas, indicating that these changes are specific to areas activated by the training (75). Furthermore, Kleim et al. (44) showed that although 30 days of training are sufficient to induce angiogenesis within motor cortex, it does not alter motor map topography.

Despite the lack of exercise-induced quantifiable increases in synaptogenesis in the motor cortex, exercise training does upregulate neurotrophic factors that promote neuronal survival and differentiation (79). Moderate motor activity, such as animals running on an unobstructed walkway for several minutes a day and voluntary exercise in a running wheel, elevates the expression of BDNF in the motor cortex (49). However, whereas skilled training induced both increases in BDNF levels and tyrosine kinase receptors, exercise only affected BDNF

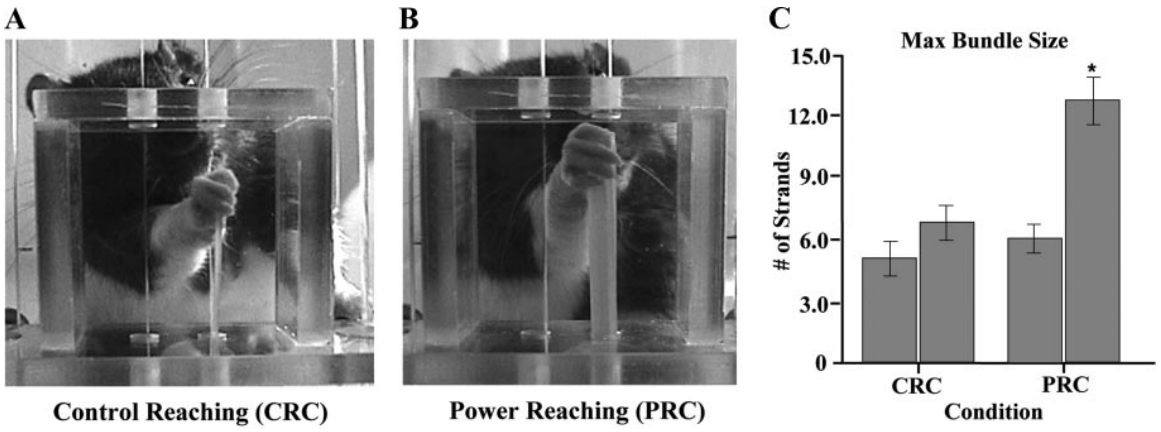

Fig. 2. *A*: animals trained in a control reaching condition (CRC) were trained to reach for a single strand of pasta for 30 days. *B:* animals in the power reaching condition (PRC) were trained to reach for progressively larger bundles of pasta. *C*: mean maximum (Max) pasta bundle size (means ± SE) broken by PRC and CRC animals. PRC animals showed a significant increase in maximum bundle size after training, whereas CRC animals did not [Student's paired *t*-test; $*P < 0.05$; see Remple (69)].

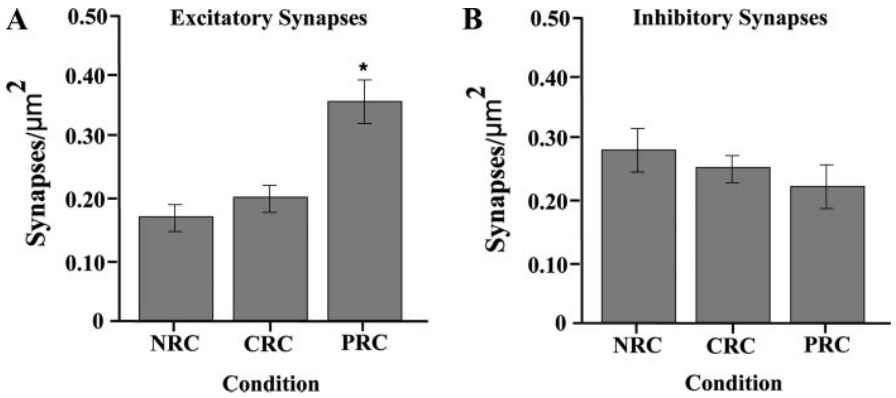

Fig. 3. Mean (± SE) number of synapses per μm^2 of soma surface onto neurons within ventral horn of cervical spinal cord. *A*: PRC ($n = 8$) animals showed a significantly higher density of excitatory axosomatic synapses than both CRC ($n = 8$) and nonreaching control (NRC; $n = 8$) animals ($F_{2,20} = 4.27$; $^*P < 0.05$). *B*: no significant differences were found on the density of inhibitory synapses between any of the 3 conditions ($F_{2,20} = 0.87$; $P > 0.05$).

levels (49). These data indicate that it is possible that exercise may act to create a more supportive and nutritive neural environment, possibly through increased vasculature, blood flow, or growth factors, but that it does not induce any significant changes in cortical circuitry.

SPINAL CORD

Skill training. Studies of skill learning have traditionally focused on supraspinal areas and have largely ignored the spinal cord. Despite its central role as the final common pathway for motor behavior, the spinal cord's contributions to motor skill remain largely unknown. However, operant conditioning of the spinal reflexes provides some insight into how learning can induce spinal cord plasticity. Wolpaw and colleagues have conducted a series of elegant experiments examining spinal cord plasticity during operant conditioning of the spinal stretch reflex (SSR) or its electrical analog, the H reflex (reviewed in Ref. 82). The SSR occurs in response to a sudden muscle stretch that is detected by muscle spindles whose afferents (Ia fibers) synapse with α-motoneurons that then synapse with the muscle. The H reflex is the electrical analog of the SSR that is elicited by electrically stimulating the Ia afferents. These experiments have shown that humans (73), monkeys (8), and rats (11) can gradually increase or decrease the SSR or the H reflex. The conditioned changes persist after spinal cord transection (83), demonstrating that the adaptation is within the cord itself.

The conditioned decrease in the H reflex is due to an increase in motoneuron firing threshold, whereas a reflex increase is due to reduced inhibition of the motoneuron (7, 8). Decreasing the H reflex causes an increase in GABAergic (inhibitory) synapses onto spinal cord (20, 80) and reduced motoneuron axon conductance (6). These changes likely reflect increased inhibition, in animals conditioned to decrease H reflex, from interneurons driven by corticospinal afferents.

Changes in spinal reflexes can also be observed during long-term training of more complex limb movements. Meyer-Lohmann et al. (54) trained monkeys for four years to make smooth repetitive arm flexion and extension movements while brief perturbations occurred at random times. The SSR to the perturbation gradually increased and took over the task of correcting the perturbation, and later reflex responses slowly disappeared. The increased SSR was also adaptive as it produced a faster and better movement corrections. People trained to walk backward for several weeks also show progressive changes in the H reflex elicited at different points in the step cycle (77). Over several weeks of training, the H reflex elicited during the stance and late-swing phases of backward locomotion is decreased without any change in soleus MEPs evoked by TMS. These data demonstrate that motor skills, at least those that are operant conditioned, induce alterations in the spinal cord. Further studies using different skilled training paradigms are necessary before the exact nature of learning-induced changes in the spinal cord will be understood.

Strength training. Changes in spinal cord circuitry, as evidenced by modifications in reflex physiology, have also been observed in association with resistance training. Whereas the H reflex is used to assess the excitability of spinal α-motoneurons and the synaptic efficacy of Ia afferents, the V-wave measures reflect the overall magnitude of efferent motor output from the α-motoneuron pool, resulting from descending central pathways. Thus the H reflex is thought to reflect spinal excitability, whereas the V wave reflects corticospinal drive. Cross-sectional studies have demonstrated H reflex excitability is reduced (53), whereas the V wave is increased (71) in power-trained athletes compared with both endurance athletes and controls. Thus power training decreases the relative number of motoneurons activated by the Ia afferent volley. However, the increased V wave indicates enhanced corticospinal input in strength-trained athletes and reflex responses may then be altered during voluntary contraction. Indeed, several weeks of strength training cause significant increases in H-reflex and V-wave amplitudes when the measurements were taken during participants' maximum voluntary contractions (1). This suggests that strength training may be associated with increased motoneuron excitability (1, 11). However, strength training also leads to decreases in TMS-evoked MEPs (9, 33). Thus the increased excitability does not appear to be mediated by enhancement of corticospinal projections as measured by TMS. However, the descending output elicited by TMS of the motor cortex certainly differs substantially from the output generated physiologically to produce voluntary movement. Strength training may lead to an enhanced capacity for motoneuron recruitment and sustained activation that is not detectable by single-pulse TMS.

To further examine the possibility that strength training alters spinal cord circuitry, we have examined the number of synapses onto neurons within the ventral horn of the cervical spinal cord of rats from a previous study examining the effects of differential motor training on motor map organization (69).

Strength-trained rats exhibited a greater number of excitatory but not inhibitory synapses onto spinal motoneurons compared with reaching and untrained controls (Fig. 3). Although the origin of these synapses is unclear, this is consistent with the notion that strength training increases motoneuron excitability. The experiment provides a double dissociation of strength training vs. skill training. Skill training induces reorganization of movement representations (69), whereas strength induces synaptogenesis within spinal cord. Thus the behavioral demands associated with each task dictate the nature and locus of the plasticity.

Endurance training. As with strength and skill training, the majority of studies examining changes in spinal cord circuitry with endurance training have examined changes in spinal reflexes. These studies have demonstrated that endurance-trained subjects have enhanced H, Achilles tendon and patellar tendon (50) reflexes. The size of the soleus H reflex also increases as a function of daily activity. It is larger in moderately active people than in sedentary people and even larger in extremely active people (59). However, the H reflex is smaller in ballet dancers than sedentary people. This finding indicates the difficulty in distinguishing between the different forms of motor training. Ballet dancing requires enhanced endurance, strength, and skill. Thus smaller H reflexes likely reflect the combination of these other forms of motor training. For example, because cocontraction of muscles is associated with greater presynaptic inhibition, the persistent cocontractions essential for skilled movement, such as in ballet dancing, may lead to lasting decrease in transmission at the Ia synapse and thus explain the reduction in H reflex. Such changes might enhance the precision of individual movements. Thus, as with motor cortex, activity alone is not the sole signal for driving spinal cord plasticity. Again, plasticity is dependent on the demands of the task rather than simply the amount of motor activity. Additionally, due to the complexity of motor repertoire, it is often difficult to clearly delineate corticospinal changes that result from each of these three forms of motor training.

THE COMPLEXITY CREATED BY EXPERIENCE-SPECIFIC PLASTICITY

It is important to point out that the inherent capacity for experience-specific plasticity within the motor system adds an additional level of complexity to the neural encoding of motor behavior. First, most new motor behaviors are acquired with some element of skill learning, increased strength, and increased endurance. Therefore, the acquisition of motor behavior is associated with specific patterns of plasticity across the motor system, which encode each element of motor output and are potentially difficult to distinguish. Second, because multiple motor behaviors are encoded within the same sites, plasticity within these sites must be layered onto or incorporated into neural circuits that have previously undergone training-induced reorganization. Thus previous experience-specific reorganization may be altered by these newly induced neural plastic changes and vice versa. This must have behavioral consequences whereby old motor behaviors may impede the acquisition of new behaviors or new behaviors may impair the performance of old behaviors. Such proactive and retroactive interference of motor behaviors has long been recognized (4, 61). Finally, plasticity at one site in response to a given training experience may itself induce plasticity upstream or downstream from that site. Such reactive plasticity may have no relationship to the recently acquired behavior, but by changing the state of the system, unrelated training experience may influence the performance of existing motor behaviors or the acquisition of new behaviors. Thus the mechanisms of encoding motor behavior may themselves have to adapt to the state of the system at the time of training. This metaplasticity is certainly overlooked in animal studies where the subjects have very limited motor experience complexity before experimentally dictated motor training. Despite these caveats, however, it is clear that motor training imparts structural and functional reorganization across the motor system, the nature of which is dictated by the behavioral demands of the training experience.

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