Task-specific hand dystonia: can too much plasticity be bad for you?

Angelo Quartarone¹, Hartwig R. Siebner² and J.C. Rothwell³

¹Department of Neuroscience, Psychiatric and Anaesthesiological Sciences, University of Messina, 98125 Messina, Italy
²Department of Neurology, Christian-Albrechts-University, 24105 Kiel, Germany
³Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College of London, London WC1N 3BG, UK

Patients with occupational hand dystonias have task-specific involuntary co-contraction and overflow of activity to inappropriate muscles. This interferes with highly skilled movements such as handwriting (writer’s cramp) or playing a musical instrument (musician’s cramp). Transcranial stimulation methods that probe mechanisms of synaptic plasticity in the motor cortex show an abnormal modifiability of sensorimotor circuits in patients with writer’s cramp, probably because homeostatic control of the range of modification is deficient. We argue that during skilled motor practice, this leads to an excessive tendency to form associations between sensory inputs and motor outputs (abnormal potentiation) and to a failure to weaken already existing associations (deficient depotentiation). Deficient homeostatic control might be an important mechanism that triggers maladaptive reorganization and produces symptoms of occupational hand dystonias.

Introduction
Plasticity refers to the ability of the nervous system to change the effectiveness of transmission in neural circuits. This can involve changes in membrane properties such as a reduction in the threshold for initiation of an action potential, or changes in the effectiveness of synaptic transmission. Although much of the work on mechanisms of plasticity has been carried out in reduced animal preparations, several non-invasive neurophysiological methods have recently been developed that enable study of plasticity at a regional level in the human brain. The majority of these have focussed on the cerebral cortex and make use of techniques involving transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (TDCS).

Neural plasticity itself is almost always regarded as a ‘useful’ phenomenon that is important in learning and memory and could potentially compensate for dysfunction after injury. The question we address here is whether pathologies of the nervous system can result in abnormal plasticity and lead to identifiable clinical states. The model we propose is focal dystonia, in which patients have involuntary muscle contractions at rest or during the performance of intended movements [1–3]. We argue that normal mechanisms of neural plasticity that are recruited after injury or during practice are subtly abnormal in some individuals. This leads to inappropriate associations between sensory input and motor output and the appearance of a characteristic movement disorder.

Clinical features and physiology of focal occupational dystonias
Dystonia can be defined as a syndrome characterized by prolonged muscle contractions that cause involuntary repetitive twisting movements and abnormal postures of the affected body parts [1]. The dystonic pattern can involve many segments of the entire body (generalized dystonia), one side of the body (hemidystonia), adjacent parts of the body (segmental dystonia) or a single body part in isolation (focal dystonia). In some focal dystonias, symptoms become apparent only if patients perform a specific motor task [4] and are absent when the same part of the body is used in a different task. For instance, in writer’s cramp the act of handwriting induces involuntary contractions of muscles in the hand, but the same patient might be able to use the hand normally when pulling on a rope with a power grip. This task specificity can be observed in other focal dystonias, such as pianist’s cramp, typist’s cramp and other cramps, which are known as occupational dystonias.

Most focal dystonias appear in adulthood, and often they do not develop until late middle age. In some patients, these dystonic conditions are associated with periods of intensive training of a particular movement. A common variety of these is musician’s dystonia, which can affect professional musicians. Historically, other occupations such as telegraphy or writing led to typist’s cramp or writer’s cramp [5]. Often the dystonia persists even if patients reduce or cease their practice regimen.

Several lines of evidence suggest that there might be a predisposing factor in some individuals that causes them to react abnormally to excessive training so that they develop task-specific hand dystonia. For example, electroencephalographic (EEG) and magnetoencephalographic (MEG) studies [6,7] of evoked responses in the somatosensory cortex of patients with focal dystonia of the hand (writer’s cramp) have revealed a less segregated representation of the individual digits in the somatosensory
homunculus than in non-dystonic subjects. This does not itself tell us whether the disorganization of the cortex caused dystonia, or whether the abnormal movements produced by the dystonia led to disorganization. However, the fact that patients who have focal dystonia in only one hand show pronounced changes in organization in both sides of the brain [8] is compatible with the idea that there are intrinsic factors that cause reorganization of cortical connections and that these predispose affected individuals to develop dystonia. This conclusion is consistent with metabolic positron emission tomography (PET) studies that have shown increased covariance of regional activity among several subcortical structures, including the lenti-form nucleus,pons and midbrain in patients who have the genetically determined DYT1 form of dystonia. The DYT1 mutation in these patients is only partially penetrant, meaning that many individuals who carry the gene have no clinical signs of dystonia. Nevertheless, Eidelberg et al. [9] found that, despite being clinically normal, individuals had the same pattern of abnormal functional coupling between brain areas as in affected patients. Again this suggests that there might be an underlying subclinical deficit that predisposes some individuals to dystonia. What is the nature of the deficit that leads to these changes in brain organization?

An animal model of aberrant plasticity leading to dystonia

In an influential study, Byl et al. [10] showed that monkeys who were over-trained to make a particular highly specific hand movement sometimes developed difficulties in moving their hands that appear similar to the problems of patients with focal hand dystonia. The somatosensory cortex of these animals was less well organized than that of healthy monkeys, with larger receptive fields and overlapping representations of the individual digits. A change in the pattern of connectivity in the sensory and motor cortices was thought to lead to inappropriate associations between inputs and outputs of the motor areas and cause errors in selecting muscles used in voluntary movement.

However, this experiment showed only that severe over-training can lead to abnormal reorganization of the sensorimotor cortex and dystonia. It does not give clues as to why in humans only some subjects develop dystonia after excessive training whereas others are completely healthy. This question was addressed by an animal model of blepharospasm, a focal dystonia affecting the muscles involved in opening or closing the eyelid.

In rats (and humans), weakening of the eyelid closing muscle, the orbicularis oculi muscle, causes an adaptive increase in the gain of the blink reflex that ensures complete closure of the eyelid even when the muscle has less strength than usual. This is an example of plasticity in a neural circuit outside the cerebral cortex, involving a relatively simple reflex arc in the brainstem. Schicatano et al. [11] gave rats a small lesion of the dopaminergic innervation of the basal ganglia, which on its own had no effect on blink reflexes. They found that if they weakened the orbicularis oculi muscle after making the lesion, then the normal process of blink adaptation was enhanced. The gain of the response grew more than necessary and led to excessive blinking in response to irritating stimuli. This eventually led to the occurrence of spontaneous blinking and blepharospasm. They suggested that the subclinical lesion affected the adaptive processes that normally control the size of the blink reflex: effectively, the plasticity of the circuit had been enhanced. Thus, it might be that focal dystonias in humans caused by excess practice or injury occur only in individuals with pre-existing abnormalities of neural plasticity. The experiments described in the next section tested this point.

Transcranial stimulation techniques to study motor cortex plasticity in humans

TMS and TDCS are methods to stimulate the cerebral cortex painlessly through the intact skull and can be used to evoke plastic changes in the motor cortex. TMS was first introduced as a method to investigate the integrity of the corticospinal outflow from cerebral motor cortex to the spinal cord [12]. The TMS pulses readily penetrate the skull and carry an electric stimulating current into the cortex near the surface. In the motor area, this leads to activation of pyramidal neurons, conduction of impulses to the spinal cord and eventually to contraction of muscles on the contralateral side of the body. Interestingly, the TMS pulses tend not to activate the pyramidal output neurons directly, but instead to stimulate the axons of neurons that synapse onto them. Thus, the size of the response produced by a given stimulus is sensitive to the excitability of synaptic connections within the cortex, giving an indirect measure of the excitability of intrinsic cortical circuits within the conscious brain. This provides a very useful measure of any changes produced by neural plasticity within the motor cortex.

In addition to probing motor cortex excitability with single pulses, TMS can also produce long-term changes in excitability if the TMS pulses are applied repetitively [13]. Three such conditioning protocols have been used and are summarized in Box 1. We will refer to these as repetitive TMS (rTMS), theta-burst stimulation (TBS) and paired associative stimulation (PAS). In all cases, the changes in excitability evoked by a conditioning TMS protocol are monitored by measuring the electromyographic (EMG) amplitude of the motor evoked potential (MEP) in response to a standard single TMS pulse. For example, such measures show that low-frequency application (1 Hz) of 1500 stimuli depresses MEPs for ~30 min after the end of rTMS, whereas high-frequency application (5 Hz) of the same number of pulses increases MEPs for a similar amount of time. Many of the changes that have been described outlast the conditioning protocol by at least 30min and can be reduced by treatment with drugs, such as dextromethorphan, that interfere with NMDA receptors. Because of this they are usually thought to involve changes in synaptic effectiveness in the stimulated cortex that are analogous to long-term depression (LTD) and long-term potentiation (LTP) in reduced preparations (‘LTP/LTD-like’ effects) [14].

One important feature of all these protocols is that the basal state of the cortex at the time of conditioning can change the long-term effects that occur. For example, the
Box 1. Inducing LTP and LTD-like effects in human motor cortex: four methods of that have been used to explore cortical plasticity in dystonia

In all cases, motor excitability is assessed by measuring the EMG response to a standard single transcranial magnetic stimulation (TMS) pulse before and at various times after the plasticity-inducing protocol. Protocols on the left of Figure I all decrease cortical excitability (blue arrow) whereas those on the right all increase excitability (red arrow). The methods in Figure I(a–c) involve repeated TMS pulses. In Figure I(a), TMS is applied at regular intervals until 1000–1500 total stimuli have been given. If the pulses are given at a frequency ≥5 Hz they facilitate whereas a frequency of 1 Hz depresses excitability for 30–60 min [13]. In Figure I(b), the TMS pulses are applied in high-frequency bursts of three pulses at 50 Hz, repeated five times per second. These are 'theta burst' paradigms, so called because the theta rhythm in EEG has a frequency of 5 Hz [50]. Bursts that are applied intermittently (2 s on, 8 s off, repeated 20 times to give 600 TMS pulses in total) cause facilitation whereas continuous theta bursts for 40 s (a total of 600 pulses) lead to suppression. Paired associative stimulation (PAS; Figure Ic) is based on descriptions of Hebbian plasticity. Each TMS pulse is applied in close temporal relation to an electrical stimulus of the median nerve at the wrist [25]. If the stimuli are timed with an interstimulus interval (ISI) of 25 ms then the afferent input from the median nerve stimulus reaches the motor cortex just before the TMS is given. In this condition, repeated pairings (usually 90–100 given every 2–3 s) lead to facilitation, whereas if the interval between pulses is 10 ms there is suppression of excitability. In transcranial direct-current stimulation (TDCS) of the brain (Figure Id), a small electrical current (1–2 mA) is applied via two electrodes placed on the scalp [16]. This is thought to depolarize cortical neurons by a few millivolts and change their firing frequency. Application using the positive terminal, or anode, over the motor cortex leads to facilitation whereas cathodal stimulation over the motor area causes suppression.

![Figure I. Four different methods of applying transcranial brain stimulation to produce long-lasting excitatory or inhibitory after-effects on the motor cortex.](image-url)
and/or motor areas of cortex. In an early study, Siebner et al. [18] applied 1800 TMS pulses at 1 Hz over the premotor area of cortex and examined the after-effect on patterns of regional neuronal activity as indexed by PET measures of regional cerebral blood flow. Premotor rTMS led to a reduction in regional neuronal activity for at least 1 h after the end of stimulation. The suppressive effect on regional neuronal activity was the same at rest and during sequential finger movements, and occurred both at the site of stimulation and at connected sites at a distance, such as the primary motor cortex and supplementary motor area. In patients with hand dystonia, the changes in activity were more pronounced than in non-dystonic subjects. It seemed that the premotor cortex and connected motor areas were reacting more strongly than normal to rTMS conditioning (Figure 1a).

There are two possible explanations for this result. One is that neural circuits in the premotor cortex are more readily modified by rTMS than normal (that is, they show increased plasticity). The other is that the premotor cortex is in a different basal state in dystonia, and that this causes it to react differently to the rTMS. Functional imaging studies have shown that the premotor cortex is more active during certain types of voluntary movement in patients with dystonia [19–21] but whether the same is true at rest is unclear. Thus, conclusions about changes in neural plasticity cannot be made with certainty.

A second series of experiments addressed this problem by examining neural plasticity directly in the primary motor cortex [22–24]. Quartarone et al. [22] used the technique of PAS (Box 1), in which afferent input elicited by electrical stimulation of the median nerve at the wrist is timed to arrive at the motor cortex just before a TMS pulse is applied [25]. When the timing between the stimuli is adjusted to be ~25 ms and if 90 pairs of pulses are applied, then there is an increase in excitability of the corticospinal output to muscles innervated by the median nerve in the hand (the thenar muscles). The effect lasts ~1 h and is somatotopically specific to the area innervated by the median nerve. PAS at 25 ms also produces a lasting increase in excitability of intracortical inhibitory circuits that generate the cortical silent period in the pre-activated muscle. Patients with focal hand dystonia had three abnormalities (Figure 1b): the amount of facilitation was larger than normal; the spatial specificity was lost so that facilitation also occurred in muscles that are innervated by the ulnar nerve; and the usual increase in the duration of the cortical silent period was absent.
The conclusion was that mechanisms that facilitate the excitability of the corticospinal output to the affected limb were abnormally reactive in patients with dystonia. The failure to strengthen cortical inhibition might relate to the finding that facilitation in patients is less focussed than normal.

Further evidence of increased plasticity of sensorimotor circuits was recently reported by Baumer et al. [26]. They used a conditioning-test paradigm to test short-latency afferent inhibition in the primary motor cortex [27], and found that 1 Hz rTMS to the somatosensory cortex attenuated short-latency afferent inhibition in patients but not in healthy subjects. Again, this is compatible with an increased susceptibility of neural circuits to change excitability following a conditioning protocol.

Abnormal plasticity has also been found in the blink-reflex circuits of the brainstem in patients with focal dystonia affecting the eyelid closing muscles. The blink reflex can be recorded bilaterally using EMG electrodes over both orbicularis oculi muscles following unilateral electrical stimulation of the supraorbital nerve. The blink reflex is potentiated for 30–60 min if the subject receives a series of 12 blinks over a 15 min period in which a short burst of high-frequency stimuli is given to the same nerve at the same time as the reflex blink [28]. If the high-frequency train occurs before the reflex blink then subsequent blinks are suppressed. We recently employed this conditioning protocol to induce plasticity in the blink-reflex circuits in patients with blepharospasm [29] and showed that there was more facilitation of the blink in patients than in healthy subjects, which is again compatible with the notion that sensorimotor plasticity is abnormally increased in patients with focal dystonia (Figure 2).

Impaired homeostatic plasticity
What drives the abnormal responsiveness of the sensorimotor cortex in focal dystonia? As pointed out by many authors, the processes of neural plasticity have to be carefully controlled [30]. Plasticity that is too easy to induce might lead to formation of unwanted associations, whereas plasticity that is too difficult to produce leads to problems in learning anything new. This is apparent if we consider increasing the excitability of neural connections that have LTP-like behaviour [31]. The positive-feedback nature of LTP carries the risk of triggering an uncontrolled increase in synaptic effectiveness that becomes potentially destabilizing, and overpowers all other inputs in the system [30]. Evidence suggests that this can be prevented by making the amount of LTP dependent on the level of activity in the postsynaptic neuron: the greater the ongoing activity, the less effective are processes leading to
LTP, whereas processes leading to LTD are enhanced. Conversely, the lower the activity of the postsynaptic neurons, the more effective are processes that lead to LTP. This is known as ‘homeostatic plasticity’ and is formalized in the model originally described by Bienenstock, Cooper and Munro [31]. Given that modifications of synaptic strength must be carefully controlled, it is possible that a failure of these mechanisms could be one factor that drives the abnormal modifiability of sensorimotor circuits in patients with dystonia.

We recently proposed a new model of homeostatic plasticity in human motor cortex [32] (Figure 3). This uses TDCS to precondition the response of the motor cortex to a subsequent period of rTMS [33]. Preconditioning of the primary motor cortex with an excitatory stimulus (10 min of anodal TDCS) leads to an increase in the inhibitory effect of 1 Hz rTMS, whereas preconditioning with a suppressive stimulus (10 min of cathodal TDCS) reverses the effect and leads to facilitation. Our question was therefore whether the after-effects of 1 Hz rTMS can be modulated to the same extent in patients with dystonia.

As in controls, we found that the relatively short period of 1 Hz rTMS used in these experiments did not produce any effect in patients with focal hand dystonia, suggesting that its subliminal effects on the motor system were similar to normal [33]. Despite this, the response to 1 Hz rTMS was unaffected by preconditioning with TDCS. Indeed, 1 Hz rTMS failed to counteract the increase in cortical excitability induced by anodal TDCS (Figure 3). This would be compatible with the idea that homeostatic mechanisms that stabilize excitability levels within a useful dynamic range are impaired in patients with writer’s cramp. We suggest that this could contribute to patients’ excessive facilitation in tests of cortical or brainstem plasticity. Their nervous system does not have the usual arsenal of adaptive mechanisms that limit the allowed level of synaptic potentiation.

Although the deficits in the physiological tests of neural plasticity are clear, we cannot immediately assert that they have a role in producing clinical symptoms unless we can show that these artificial paradigms interact with natural behaviours in a useful way. Two recent studies suggest that this is indeed the case. In healthy volunteers, changes in motor cortex plasticity induced by TMS paradigms interact with learning of simple motor tasks in a manner expected of homeostatic plasticity. Ziemann et al. [34] and Stefan et al. [35] tested how a short period of behavioural motor learning changed the amount of plasticity induced by a standard PAS method. They found that the amount of facilitatory PAS (with an interval of 25 ms between median nerve and cortical stimulation)
was reduced after learning whereas the amount of inhibitory PAS (with an interval of 10 ms) was increased. The result was compatible with that expected from the rule of homeostatic plasticity proposed by Bienenstock, Cooper and Munro: after a period of increased activity it is easier to strengthen inhibitory effects and more difficult to strengthen excitatory effects.

Given these observations in healthy volunteers, it is conceivable that the abnormalities of plasticity that we have described in patients with focal dystonia will translate into clinical changes. Under normal conditions, it is likely that a fine regulation of synaptic strength reduces behavioural interference between overlapping motor tasks, thus avoiding the consolidation of movement combinations that are not wanted. When this process goes wrong, it leads to interference between tasks and action-induced dystonia.

**Implications for current concepts of the pathophysiology of focal dystonia**

Many physiological studies in patients with dystonia have indicated that there is reduced excitability of inhibitory mechanisms in spinal cord, brainstem and cortex [36]. This is complemented by imaging studies that show lower than normal GABA levels in the sensorimotor area of patients with hand dystonia [37]. Reduced inhibition in the sensorimotor system would lead to failure to suppress unintended movements of nearby muscles when a focal movement is being performed [38]. Our hypothesis does not question the role of impaired inhibition; indeed, it is well recognized that GABA-mediated inhibition is an important controller of synaptic plasticity in the cortex. Reduced GABA activity could well contribute to the excess plasticity that has been seen [39] and to the general problems in selection of movements.

Our model of disordered plasticity is also consistent with current concepts of the ‘endophenotype’ of focal dystonias that results in an increased susceptibility to the disorder [8,40]. Faulty homeostatic control of plasticity is likely to be one of several endophenotypes that could predispose towards development of dystonia. Indeed, a recent result from Edwards et al. [41] suggests that reduced susceptibility to probes of neural plasticity might even protect against development of clinical dystonia in individuals who carry multiple endophenotypes.

Although all these approaches produce some improvement in the short term, it is still unclear how lasting the benefits will be. In some cases, patients remain improved for many months or years, whereas in others the effects are transient. Our hypothesis is that if the primary disorder is one of homeostatic regulation of neural plasticity, this will predispose individuals to relapse to dystonia, particularly if the system is stressed by further excess practice. The implication is that retraining should be monitored carefully to track whether or not it is beginning to induce excessive plastic change in the motor system. If this begins to occur, then there might be a danger that homeostatic mechanisms will fail to compensate, and that at some point in the future the system will be provoked to develop dystonia.

**Implications and conclusions**

It should be noted that we do not assume that all forms of focal dystonia will show exactly the same patterns of abnormal plasticity. This is because there is good evidence that patient subgroups have differences in other physiological parameters that have been measured. For example, most idiopathic cases of focal dystonia have a mildly reduced sensory discrimination on the fingertips whereas cases of DYT1 dystonia do not [45]. Similarly, the motor cortex of patients with writer’s cramp is less sensitive than normal to afferent input from the hand, whereas the opposite is true of patients with musician’s dystonia [46]. Thus it might emerge that particular mechanisms of plasticity are affected in different subgroups of individuals.

We also note that, because focal dystonia is thought to be a disorder of the basal ganglia, it is unlikely to be the only condition to involve a disorder of neural plasticity. Recent work in animals suggests that abnormalities in the dopamine-mediated control of plasticity at corticostratial synapses might be relevant to production of L-DOPA-induced dyskinesias in Parkinson’s disease [47]. There is also evidence that plasticity of premotor and motor cortex as evaluated using rTMS [48] and PAS [49] might be abnormal in Parkinson’s disease. The role of disordered neural plasticity in patients with movement disorders might be far more common than previously anticipated.

**References**


18 Siebner, H.R. et al. (2003) Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain* 126, 2710–2725

19 Ceballos-Baumann, A.O. et al. (1995) Botulinum toxin does not reverse the cortical dysfunction associated with writer’s cramp. A PET study. *Brain* 120, 571–582


46 Rosenkranz, K. et al. (2005) Pathophysiological differences between musician’s dystonia and writer’s cramp. *Brain* 128, 918–931


