ACTA PHYSIOLOGICA

Acta Physiol 2012, **206**, 160–163

Editorial

Dystonia – a disorder of dynamics of brain plasticity modulation?

Dystonia is a medical term given to a group of syndromes characterized by continuous involuntary muscle contractions causing twisting and twitching of affected body parts in a way that does not resemble purposeful movements (Fahn *et al.* 1998). Dystonic movements may be either focal (affecting isolated body parts, e.g. face, neck and hand), segmental (affecting neighbouring body parts) or generalized (affecting whole body) (Tarsy & Simon 2006). The physiological hallmark of a dystonic movement is co-contraction of agonist and antagonist muscles that can be clearly seen in electromyographic (EMG) recordings from the affected muscles (Berardelli *et al.* 1998).

Dystonic movements can occur spontaneously, they can be triggered by arousal or movements of affected or other body parts, but on rare occasions they can be triggered only by certain purposeful actions of affected body part. One of the most prominent examples of these so-called task-specific dystonias is writer's cramp or graphospasm. In this disorder, tonic twisting movements of fingers and hand happen only during writing or even on attempts to write. Occasionally, similar symptoms may occur with other precise hand tasks. Although not as common as other forms of dystonia, such as cervical dystonia (torticollis) or generalized dystonia, due to ease of study of the muscles involved and their convenient central cortical representations at the lateral convexity of the cerebral hemispheres, writer's cramp and hand dystonia in general have been the most studied models of dystonia in physiology.

Occurrence of dystonia has been described following some brain lesions, but in the majority of cases, no structural lesion can be found (Elia *et al.* 2010). All available knowledge points towards a disorder of synaptic connections and neuronal circuits as the principal pathological substrate of dystonia. Thus, dystonia can be considered as more or less a pure disorder of function – a disorder of central nervous system (CNS) software, with apparently intact hardware. Consequently, the major insights regarding the neurobiology of dystonia have been gathered by functional investigational methods, functional neuroimaging and neurophysiological methods.

Functional neuroimaging by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have frequently shown an overactivation of primary and secondary motor cortices during performance of dystonic movements (Neychev *et al.* 2011). This was complemented by findings from neurophysiological studies that showed impaired inhibition at several levels of motor system, abnormal sensory-motor integration and probably most importantly the altered plasticity of the motor cortex (Quartarone *et al.* 2008b).

Brain plasticity is usually defined as capability of the central nervous system to optimize its activity in keeping with demands from environment (Doyon & Benali 2005). The activity can be modulated on either a cellular or system level, or both (Butz *et al.* 2009). On a cellular level, there are several mechanisms that may work in concert. They can be either short term, quick to develop and to dissolve, such as activation of latent horizontal synaptic connections, change in synaptic effectiveness and change in neuronal membrane excitability; or longer term, delayed and more enduring such as changes in dendrite morphology and in synaptic density. On a system level, the activity can be modulated either by reorganization of intracortical and other interneuronal connections or by changes in cortical, striatal, thalamic and other representational areas.

Development of transcranial magnetic stimulation (TMS) has allowed the study of human cortical plasticity in vivo. Using paired associative stimulation (PAS) protocol that consisted of a train of transcranial magnetic stimulation (TMS) pulses preceded at the fixed interval by peripheral electrical pulses delivered at the somatotopically congruent peripheral nerve, both long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity of the sensory-motor corticospinal systems were found to be abnormally enhanced in hand muscles of patients with hand dystonia (Quartarone *et al.* 2003, Weise *et al.* 2006). The finding was corroborated by results obtained by PET that the effects of another TMS-based neuromodulatory procedure, repetitive TMS (rTMS), were significantly larger in patients with hand dystonia than in healthy controls (Siebner *et al.* 2003). Moreover, the abnormality was even found in hand muscles of patients with focal dystonia affecting other remote body parts in whom hand muscles did not display any symptoms, that is, cranial and cervical dystonias, suggesting that the impairment could be a generalized feature of the condition (Quartarone *et al.* 2008a). Also, while PAS-induced sensory-motor plasticity in healthy people has quite clear topographical and

anatomical selectivity (i.e. the effect is only seen for cortical representation of the target muscle, whereas cortical representations of other muscles do not display any change), in hand dystonia patients the plasticity appears topographically disorganized (i.e. the PAS effect is seen not only for cortical representations of the target muscles, but almost equally for neighbouring muscles that have not been targeted by the neuromodulatory procedure) (Weise *et al.* 2006, 2011). The role of abnormally enhanced motor cortex plasticity in generation of dystonic symptoms was further confirmed by findings with after another TMS-based neuromodulatory procedure, theta-burst stimulation (TBS), that showed abnormally enhanced plasticity in the motor cortex only in sporadic dystonia cases and manifesting dystonia gene (DYT1) carriers, but not in nonmanifesting gene carriers; nonmanifesting gene carriers in fact had reduced plasticity (Edwards *et al.* 2006). Furthermore, deep brain stimulation of the globus pallidus, which typically ameliorates symptoms of dystonia, was found to abolish enhanced plasticity (and even led to reduced plasticity instead) (Tisch *et al.* 2007).

Another, closely related, physiological abnormality that has been also described by TMS is the presence of altered motor cortex representations of the hand muscles. The abnormality also seems to be a generalized feature of dystonia because it has been found not only in writer's cramp (Byrnes *et al.* 1998, Schabrun *et al.* 2009), but also in cervical dystonia patients (Thickbroom *et al.* 2003). Cortical representations of individual muscles are much larger, they overlap more, and their centres of gravity are much closer in patients than they are in healthy people. These results are very much in keeping with magnetoencephalography (MEG) findings of aberrant cortical sensory maps of the dystonic hand fingers in patients with writer's cramp. Similarly to the motor maps, the sensory maps overlapped significantly, particularly for the fingers I, II and III, the ones which are affected the most by dystonic movements (Bara-Jimenez *et al.* 1998, Nelson *et al.* 2009). The feature, however, seems not to be restricted to the dystonic hand, but could be seen for asymptomatic hand as well (Meunier *et al.* 2001).

However, typical design of most of the physiological studies dealing with dystonia has been to compare dystonic subjects with healthy controls, or sometimes to compare various subgroups (subtypes) of dystonia among themselves. The evidence gathered this way was static; it did not capture the dynamics of physiological interactions happening in the dystonic motor cortex. In other words, it was difficult to explain, based on that evidence only, why in the presence of the same physiological deficit, symptoms may be present in some situations but not in others or symptoms are more expressed in some situations than the others, as for example in task-specific dystonias.

Rare are the studies that tried to distinguish physiological mechanisms operational during dystonic or task-specific (potentially dyskinesiogenic) movements either by comparing them with other, clinically neutral, movements or by studying the time dynamics of physiological features during execution of a movement. For example, Filipović *et al.* (1997) showed that cortical inhibition in writer's cramp is impaired during writing tasks, but not necessarily during simple aimless contractions of the same muscle with the similar force, while Beck *et al.* (2008) showed that motor cortex inhibition in hand dystonia is selectively impaired at the initiation phase of a movement.

In line with this, Tyč, Boyadjian, Allam and Brasil-Neto, in the paper presented in this issue (Tyč *et al.* 2012), and in the accompanying paper published last year (Boyadjian *et al.* 2011), for the first time, provided evidence for differential impairment of plasticity during the performance of various tasks, potentially dyskinesiogenic and neutral ones. In the paper published in this journal last year, Boyadjian *et al.* (2011) showed, in a sample of writer's cramp patients, an abnormal increase in facilitation of a hand muscle (first dorsal interosseus) when a proximal muscle (deltoid) was co-activated, the feature that was not present during simple isolated activation of hand muscles. In this issue's paper, also dealing with writer's cramp patients, Tyč *et al.* (2012) not only corroborated findings from previous studies on abnormal motor cortical representations of hand muscles, but by extending their investigation beyond the affected area, they showed that similar dysfunction exists in more proximal muscles, such as deltoid, as well. Notwithstanding how interesting this finding was by itself, much more significant was finding that the abnormality of the cortical maps became considerably more pronounced during co-contraction of deltoid and hand muscles than it had been during isolated contraction of each of the hand muscles, even with the same strength.

These findings represent a significant step forward in further understanding the physiology of dystonia. More similar studies are needed to establish a detailed functional map of dynamic interactions operational in generation of dystonic symptoms. The knowledge should help not only in better understanding of dystonia physiology, but in designing better approaches for rehabilitation techniques aimed at suppressing the aberrant connections and re-establishing the normal ones (Rosenkranz *et al.* 2008). There has been a renewed interest in developing new rehabilitation approaches for writer's cramp and other hand dystonias (Zeuner & Molloy 2008). Given the much better and relatively unambiguous knowledge on the features

of sensory abnormalities, attempts based mainly on improving sensory discrimination and at restitution of normal central finger sensory representations have shown quite clear clinical benefits, albeit the effects were not long-lived or the treatment programmes were quite long and laborious (e.g. Zeuner *et al.* 2002, Candia *et al.* 2003). In contrast, given the much higher complexity of the motor cortex impairments and our present lack of knowledge of their dynamics, attempts at motor re-training have been developed mainly empirically and thus returned ambiguous results (e.g. Schenk *et al.* 2004, Zeuner *et al.* 2005). It is reasonable to expect that retraining approaches that would take into account dynamics of motor cortex plasticity should yield much better effects.

Conflict of Interest

None.

SF was supported by Project Grant from Serbian Ministry for Education and Science (175012).

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