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Reflex Mechanisms in CRPS-Related Dystonia

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Abstract. This paper focuses on the pathophysiology of fixed dystonia (i.e., sustained muscle contractions resulting in abnormal postures) in Complex Regional Pain Syndrome from an engineering point of view. Although the mechanisms are still elusive, the evidence implicating involvement of aberrant muscle force feedback is compelling. A neuromuscular model with aberrant muscle force feedback successfully mimicked fixed dystonia while results of several experiments point to involvement of muscle force feedback.

1 Introduction

The research described in this paper was part of the Assessment Instruments research line within TREND, a Dutch consortium of academic medical centers, universities of technology and industrial companies. TREND integrated research on Complex Regional Pain Syndrome (CRPS) type I to develop concepts on disease mechanisms that occur in response to tissue injury and methods for its assessment and treatment. Therefore, techniques were developed and evaluated within the conceptual framework regarding peripheral inflammation and central sensitization.

The aims were twofold: 1. To provide information that may elucidate the involvement of underlying mechanisms of CRPS; 2. To provide objective outcomes that reflect a particular impairment and can be used in clinical studies of patients with CRPS.

In this paper we discuss several motor control studies performed within this research line and summarize and relate their results and conclusions.

2 Materials and Methods

A non-linear computational neuromuscular model was developed to simulate fixed dystonia [1, 2] and several measurement protocols were executed to validate the neuromuscular modeling results [3–5]. Transient (time domain) and continuous

This research was performed within TREND (Trauma Related Neuronal Dysfunction), a knowledge consortium that integrates research on Complex Regional Pain Syndrome type I. The project was supported by a Dutch Government grant (BSIK03016).

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(frequency domain) approaches assessed spinal motor control by quantifying proprioceptive reflexes at the wrist in CRPS-patients. A sensory weighting study assessed the sensory motor integration of afferent feedback along the spinal-cortical pathways.

3 Results

3.1 Fixed Dystonia Cannot Be Explained Through Hyperreflexia of Muscle Spindle Feedback

One of the main findings of [6] was that CRPS-patients with fixed dystonia were (almost) unable to adopt negative Muscle Spindle (MS) feedback gains (n = 9). Positive feedback gains result primarily from monosynaptic feedback of muscle spindle afferents to the motoneurons. The strength of the afferent information can be reduced by presynaptic inhibition, which effectively decreases the feedback gains [7]. The neural mechanism for negative feedback gains must have either an inhibitory effect on the agonistic motoneuron (autogenic inhibition), an excitatory effect on the antagonistic motoneuron (reciprocal excitation), or both. Literature describing the aforementioned paths are scarce; one elaborate review mentioned only the interneuronal circuits that mediate postsynaptic inhibition of the motoneuron [8].

In an experiment using ramp-and-hold perturbations [3] it was concluded that the reflex responses were smaller in CRPS-patients with dystonia than in controls, when compared at equal contraction torques. This is in accordance with the reduced velocity feedback gain as was found in patients with dystonia in respect to controls in [4] and with previous literature that suggested that dystonic subjects have diminished perception of Ia-afferent discharges [9].

Hyperreflexia of MS feedback, commonly hypothesized to cause fixed dystonia, was not found in CRPS-patients with dystonia and is not a likely pathophysiology.

3.2 Fixed Dystonia Can Be Explained Through Aberrant Golgi Tendon Organ Feedback

The neuromuscular model mentioned in Sect. 2 showed that an imbalance in excitatory muscle force feedback from Golgi Tendon Organs (GTO) can explain the motor behavior as encountered in CRPS-related dystonia [1, 2]. Unstable excitatory muscle force feedback resulted in sustained cocontraction, increased stiffness, loss of voluntary control and activity-aggravation. With an imbalance in the force feedback between the agonist and antagonist also the abnormal posture arose, completing the five features that define the phenotype of fixed dystonia.

CRPS-related dystonia generally progresses in the extremities from distal to proximal musculature [10]. Note that the current hypothesis explains this progression with progressively diminishing central inhibition. The neural time delay of muscle force feedback is larger for distal joints, as the loop delay is directly related to the length of the feedback path. Larger time delays result in smaller stability margins and consequently instability, which will first present in distal joints and progress proximally with further increasing feedback strengths due to disinhibition.

3.3 Patients with Fixed Dystonia Have Reduced Inhibitory Golgi Tendon Organ Feedback

An experiment using system identification [4] showed significantly less inhibitory GTO feedback during force tasks in CRPS-patients with (mild) dystonia (n = 15) and dystonia-patients without CRPS (n = 10) in respect to healthy controls (n = 10) and CRPS-patients without dystonia (n = 10).

Given the syndrome's ability to progress from distal to proximal joints, but also from one extremity to another, it is likely to be of central origin (central sensitization). Several patients performed the experiment on their unaffected side where similar changes in motor adaptation were found; a finding that is in concordance with previous literature that reported force control impairment at clinically uninvolved joints in patients with focal hand dystonia [11].

The experimentally found reduced inhibitory GTO feedback in patients with relatively mild dystonia, together with the neuromuscular model's requirement of excitatory GTO feedback, is a strong indication of involvement of GTO feedback in fixed dystonia.

3.4 Patients with Fixed Dystonia Bias Sensory Weighting of Force and Position Toward Position

A sensory weighting paradigm was developed to determine how humans integrate force and position feedback to a single estimate of the current position or force. It was hypothesized that if force feedback is impaired in patients with fixed dystonia it would be weighted less. Indeed, CRPS-patients with fixed dystonia weighted position feedback heavier (n = 10) relative to healthy controls (n = 10) [5]. This is another indication of involvement of GTO feedback in fixed dystonia.

4 Discussion

An interesting notion of the non-linear neuromuscular model is that the hyperreflexia that literature proposed to cause fixed dystonia may apply to overexcitation of GTO instead of MS feedback. Although the mechanism behind CRPS is still elusive, the evidence implicating involvement of inhibitory interneuronal circuits in the pathophysiology of fixed dystonia in patients with CRPS is compelling [12]. The results are promising, but an accurate objective measure of the severity of the dystonia at the time of participation is required and test-retests need to be performed.

System identification and neuromuscular modeling are complex techniques. Simpler tests, that are unable to identify the affected motor control components, may complement such techniques and still have good predictive values or clinical relevance. For example, it has been shown that during single joint isometric tasks the variance in force exertion increased with childhood dystonia due to cerebral palsy [13].

5 Conclusions

The application of (control) engineering techniques in the field of neuroscience is promising as it allows quantification of spinal reflexes and helps understand their function. In vivo experiments on humans using continuous force perturbations quantify our ability to adapt motor control. Subsequent neuromuscular modeling and parameter estimation yield deeper insights into the underlying mechanisms. Compelling evidence suggests involvement of muscle force feedback from Golgi tendon organs in fixed dystonia as presents in CRPS. A neuromuscular model with aberrant muscle force feedback successfully mimicked behavior resembling dystonia, while experiments demonstrated a lack of inhibitory muscle force feedback in CRPS-patients with fixed dystonia during a force-control task. Additionally, sensory weighting in CRPS-patients with fixed dystonia was biased toward position control, indicative of unreliable force feedback. This research elucidates the mechanisms of fixed dystonia and may in time develop into a diagnostic tool that objectively quantifies fixed dystonia, expediting diagnosis and monitoring its progression.

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