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Modeling movement disorders—CRPS-related dystonia explained by abnormal proprioceptive reflexes

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ABSTRACT

Humans control their movements using adaptive proprioceptive feedback from muscle afferents. The interaction between proprioceptive reflexes and biomechanical properties of the limb is essential in understanding the etiology of movement disorders. A non-linear neuromuscular model of the wrist incorporating muscle dynamics and neural control was developed to test hypotheses on fixed dystonia. Dystonia entails sustained muscle contractions resulting in abnormal postures. Lack of inhibition is often hypothesized to result in hyperreflexia (exaggerated reflexes), which may cause fixed dystonia. In this study the model-simulated behavior in case of several abnormal reflex settings was compared to the clinical features of dystonia: abnormal posture, sustained muscle contraction, increased stiffness, diminished voluntary control and activity-aggravation.

The simulation results were rated to criteria based on characteristic features of dystonia. Three abnormal reflex scenarios were tested: (1) increased reflex sensitivity—increased sensitivity of both the agonistic and antagonistic reflex pathways; (2) imbalanced reflex offset—a static offset to the reflex pathways on the agonistic side only; and (3) imbalanced reflex sensitivity—increased sensitivity of only the agonistic reflex pathways.

Increased reflex sensitivity did not fully account for the features of dystonia, despite distinct motor dysfunction, since no abnormal postures occurred. Although imbalanced reflex offset did result in an abnormal posture, it could not satisfy other criteria. Nevertheless, imbalanced reflex sensitivity with unstable force feedback in one of the antagonists closely resembled all features of dystonia. The developed neuromuscular model is an effective tool to test hypotheses on the underlying pathophysiology of movement disorders.

1. Introduction

Movement disorders impair the control of body parts (segmental or focal) or the whole body (general) and can be recognized on the basis of characteristic clinical features. Since substantial overlap in features exists between movement disorders, diagnosis can be difficult, especially as multiple movement disorders may coexist (Edwards et al., 2003). The underlying mechanisms of movement disorders are poorly understood, which hampers the development of diagnostic tools.

Neuromuscular modeling can help understand the pathophysiology of movement disorders like fixed dystonia, a movement disorder characterized by abnormal postures and sustained muscle contractions. The central nervous system (CNS) interacts with the musculoskeletal system and receives feedback from a variety of interacting feedback pathways: visual, vestibular, tactile and proprioceptive (from muscle spindles and Golgi tendon organs), which makes for a closed-loop configuration in which cause and effect are hard to recognize (Ludvig and Kearney, 2009; Van der Helm et al., 2002; Van der Kooij and Van der Helm, 2005). Pinpointing the initiating mechanisms of disorders is impossible without a thorough understanding on how the components of the neuromuscular system interact. Tools from the field of control engineering have been successfully applied to estimate the contribution of the individual components of the neuromuscular system (e.g., Kearney et al., 1997; Kiemel et al., 2006; Schouten et al., 2003). To understand the underlying mechanisms of motor control, neuromuscular models have been developed that range from control theoretical in the form of transfer functions (e.g. Peterka, 2002; Schouten et al., 2008) to

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physiological or interacting spiking neurons (Bashor, 1998; Stienen et al., 2007). Muscle models range in complexity from springs that describe the force–length and force–velocity characteristics (Hill, 1938; Winters and Stark, 1985) to finite-element models (Van der Linden et al., 1995; Yucesoy et al., 2002). Only models that include both the neural controller and the musculoskeletal system like in Winters (1995) capture their interaction, likely an important aspect in movement disorders.

In this study, non-linear neuromuscular modeling of the wrist was applied to fixed dystonia, which served as an example to demonstrate the merit of the modeling approach in understanding the pathophysiology of movement disorders. Model-simulated behavior was systematically assessed for several abnormal reflex scenarios and compared with the clinical features of fixed dystonia to shed light on the underlying pathophysiology.

Dystonia is characterized by involuntary sustained muscle contractions of one or more muscles, frequently causing repetitive movements, or abnormal postures (Fahn and Eldridge, 1976; Jankovic, 2007; Marsden and Rothwell, 1987). Contrary to primary (idiopathic) dystonia, which is generally characterized by slow, repetitive or twisting movements, secondary (symptomatic) dystonia in complex regional pain syndrome (CRPS) is characterized by fixed postures (fixed dystonia) (Albanese et al., 2006; Munts et al., 2011; Schwartzman and Kerrigan, 1990). Literature suggests that reduced inhibition in the motor system (Tarsy and Simon, 2006) leads to continuously activated muscles due to hyperreflexia, i.e. over-excited reflexes (Birklein et al., 2000; Schwarzman and Kerrigan, 1990; Van de Beek et al., 2002; Van Hilten et al., 2005). Although an association of dystonia due to cerebral palsy with reflexive muscle activation has been described (Van Doornik et al., 2009), recent work on CRPS-related fixed dystonia did not find hyperreflexia (Mugge et al., in press). If dystonia is caused by abnormal proprioceptive reflexes, its etiology is likely not as straightforward as hyperreflexia.

The goal of this study is to develop a neuromuscular model to test hypotheses on movement disorders. The case study aims to appoint proprioceptive mechanisms that are likely to be involved in fixed dystonia. A better understanding of the mechanism causing dystonia can aid diagnosis and treatment.

2. Method

2.1. Neuromuscular model

The 1-DOF neuromuscular model of the human wrist consists of two antagonistic Hill-type muscles with spinal proprioceptive feedback pathways, see Fig. 1. The muscle model includes a contractile (CE), a series elastic (SE) and a parallel (PE) element (Winters and Stark, 1985) and was implemented into Simulink (Matlab, Mathworks); details provided in Appendix A. The muscle receives voluntary input from supraspinal structures and input from the proprioceptive reflex pathways (velocity, position and force feedback), representing the Ia, II and Ib afferents. Inputs to the model are the voluntary muscle commands and the external torque acting on the limb. Reflex strengths are implemented as muscle-specific feedback gains, in series with a transport delay representing neural latency. Note that the non-linear nature of the model enables feedback gains to be imbalanced (unequal between antagonists) and limits unstable feedback through saturation of the neural signal. Position and velocity feedback are unidirectional, measuring only elongation of the muscle.

Tables 1 and 2 present the model parameters. The muscle parameters are based on morphological data adapted from Winters and Stark (1985). The reflex strengths were set such that each of the reflex pathways affected the step response about equally. A sensitivity analysis was performed to assess the robustness of the findings by determining the effect of the nominal parameter values on the simulated motor behavior. Reflexes assist to maintain posture and modulate during external force and voluntary movement (Johnson et al., 1993). To simulate reflex maladaptivity, all reflex modulation was excluded in the model, so that both externally applied forces and voluntary movements elicited reflexes.

2.2. Case: fixed dystonia

To evaluate the limb response to external torques and voluntary activation, each simulation run was divided into four sections of 5 s. During the first section a constant external torque was applied to the limb without voluntary activation. During the third section one muscle was voluntarily contracted. During the second and the fourth section no inputs were given to assess whether the limb returned to its initial state. Outcome measures were derived from the joint angle and contraction levels over the last second of each section to exclude effects of dynamics. If the dynamics were too slow to stabilize the joint within 5 s, the section was extended to 10 s.

2.2.1. Abnormal reflex scenarios

Reflex pathways were made hypersensitive to mimic reduced inhibition. Three abnormal reflex scenarios were separately analyzed for each of the reflex pathways (position, velocity and force): (1) increased reflex sensitivity, where the sensitivity of both the agonistic and the antagonistic reflex pathways are equally increased, (2) imbalanced reflex offset, where a static offset is added to the reflex

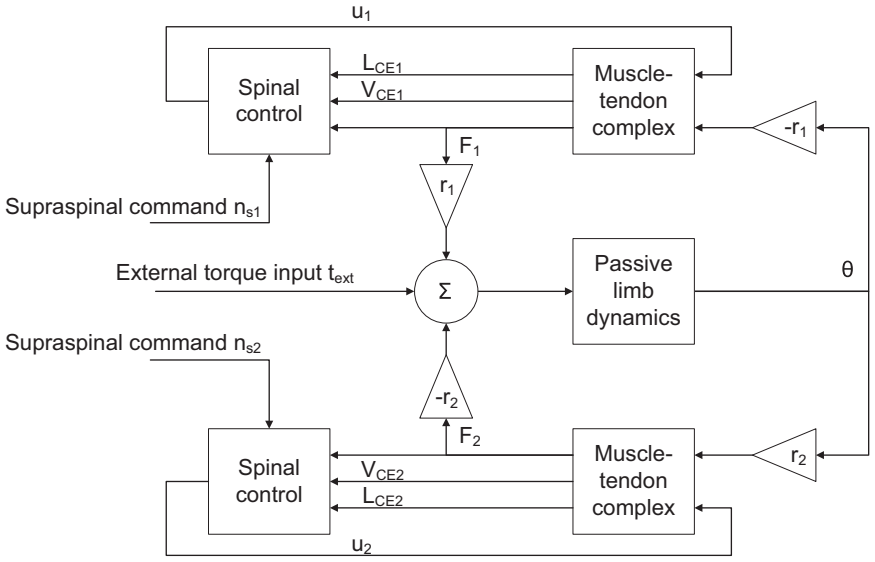

Fig. 1. Schematic representation of the model structure. Parameters and states belonging to the agonist are indicated by a subscripted 1 and to the antagonist by a subscripted 2. Inputs are an external torque to the limb (t_{ext}) and voluntary muscle commands to the antagonists (n_s). The joint angle (θ) is fed back through passive dynamics of the limb, passive dynamics of the muscle and through active responses via reflex pathways. Triangular blocks represent moment arms (r) and square blocks represent muscle and neural control dynamics. Neural input to the muscle (u) is based on muscle stretch L_{CE}, muscle stretch velocity V_{CE} and muscle force F. Appendix A describes the muscle model in detail. Parameter values are presented in Tables 1 and 2.

pathways on the agonistic side only and (3) imbalanced reflex sensitivity, where the sensitivity of only the agonistic reflex pathway is increased (Fig. 2).

2.2.2. Criteria for fixed dystonia and outcome measures

The definition of dystonia as given by Xia and Bush (2007) is "a neurological movement disorder characterized by prolonged, repetitive muscle contractions that may cause sustained twisting movements and abnormal postures". However because of the lack of specific diagnostic tests, guidelines or systematic reviews (Albanese et al., 2006) different types of dystonia exist that may very well have various pathophysiologies. This study narrows down to the fixed phenotype of dystonia as encountered in CRPS.

Table 1
Constant parameter values of the wrist model.[a]

Parameter	Value	Description
Reflexes		
τ_{ms}	0.025	Reflex latency of muscle spindle feedback (s)
τ_{gto}	0.025	Reflex latency of Golgi tendon organ feedback (s)
Muscle		
F_{max}	1000	Maximum muscle force scaling factor (N)
r	0.02	Muscle moment arm (m)
b_{pas}	0.1	Passive limb damping (Nms/rad)
k_{pas}	1	Passive limb stiffness (Nm/rad)
m	0.006	Limb inertia (kg m^2)
De-/activation		
τ_{ex}	0.03	Excitation dynamics time constant (s)
τ_{ac}	0.005	Activation dynamics time constant (s)
τ_{da}	0.03	Deactivation dynamics time constant (s)
Scaling		
L_{m0}	0.2	Zero length of the muscle (m)
Force–velocity CE		
V_{vm}	3	Unloaded maximum contractile element velocity (m/s)
V_{er}	0.5	Constant
V_{ml}	1.3	Constant
V_{shl}	0.5	Slope parameter
V_{sh}	0.25	Hill shape parameter (−)
Force–length CE		
L_{cesh}	$0.25L_{m0}$	Shaping parameter of the contractile element (m)
Force–length SE		
SE_{sh}	3	Shaping parameter of the series elastic element (−)
SE_{xm}	$0.05L_{m0}$	Maximum SE length (m)
L_{ce0}	$0.75L_{m0}$	Zero length of the contractile element (m)
L_t	$0.25L_{m0}$	Zero length of the tendon (m)
Force–length PE		
PE_{sh}	3	Shape parameter of the passive element, with a higher value resulting in higher curve concavity (−)
PE_{xm}	$0.4L_{m0}$	Displacement at maximum torque (m)
L_{pe0}	L_{m0}	Zero length of the passive element (m)

[a] CE, SE, PE and activation parameters adopted from Stroeve (1996) (based on Winters and Stark, 1985); muscle parameters, reflex latencies and scaling were estimated.

The simulated behavior was rated to five criteria. Three criteria were extracted from the definition:

1. Abnormal posture: a fixed posture away from the limb's neutral position, but not necessarily at the joint's extreme, as stated by Van Doornik et al. (2009): "This mid-range posture is an important aspect of fixed dystonia and suggests feedback stabilization". Albanese et al. (2006) stated that dystonic postures can persist without appearance of dystonic movements and that the muscle contractions have a consistent posture-assuming character. In this simulation study, the posture outcome measure was the joint angle in the section where no input was given.
2. Sustained muscle coactivation: simultaneous tonic activation of agonistic muscles (Albanese and Lalli, 2009; Quartarone et al., 2008; Yanagisawa and Goto, 1971). Here, the coactivation outcome measure was the lowest active torque of the two muscles during voluntary antagonist muscle activation.
3. Increased joint stiffness: resistance to movement which is caused by both muscle coactivation and reflexive feedback. Albanese and Lalli (2009) list "a sensation of rigidity and traction is present in the affected part" as one of the clinical criteria for the physical signs observed in patients with dystonia. Here, the stiffness outcome measure was the ratio between the applied torque and the resulting displacement of the limb, which is the difference between the joint angle in the section where no input was given and the section where an external torque was applied.

Two additional criteria were defined based on clinical experience and literature (Van de Beek et al., 2002; Van Hilten et al., 2001, 2005):

4. Diminished capacity for voluntary control: the limb cannot voluntarily be moved out of its fixed posture and no considerable joint torques can be produced (Mugge et al., in press) leading to disability (Geyer and Bressman, 2006).

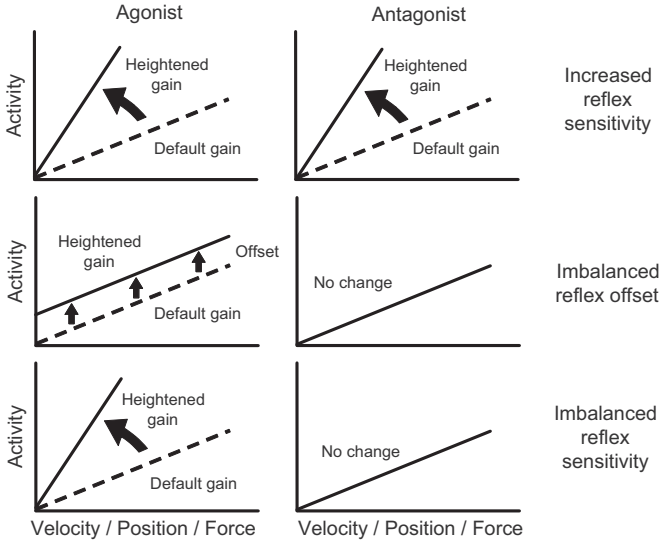

Fig. 2. Schematic representation of the abnormal reflex scenarios tested with the neuromuscular model. increased reflex sensitivity, increased sensitivity of both the agonistic and the antagonistic reflex pathways; imbalanced reflex offset, an offset to the reflex output in only the agonistic reflex pathways; and imbalanced reflex sensitivity, increased sensitivity of only the agonistic reflex pathways.

Table 2
Variable parameter values of the wrist model.

Parameter	Default value	Multiplication factors	Description
Reflexes			
k_p	1	1, 2, 3, 5, 10, 50	Position feedback gain/sensitivity (−)
k_v	0.1	1, 2, 3, 5, 10, 50	Velocity feedback gain/sensitivity (−)
k_f	0.0004[a]	1, 1.5, 2, 2.5, 3, 3.5, 5, 10, 50	Force feedback gain/sensitivity (−)
Bias	0.1	0.5, 1, 2, 3, 5	Offset to the output of the proprioceptive feedback
Voluntary/external			
	On	Off	First section voluntary off and external on, third section voluntary on and external off
n_s	0.1	0	Voluntary supraspinal input to the muscle [0…1]
t_{ext}	1	0	External torque applied to the limb (Nm)

[a] Note that the force feedback loop gain is scaled with the maximum muscle force scaling factor F_{max}. Unstable force feedback occurs when the force feedback loop gain is beyond unity, which means with $F_{max}=1000$ N that $k_f > 2.5$ results in instability.

Here, the voluntary control outcome measure was the change in joint angle from rest to the voluntary contraction.

5. Activity-aggravation: use of the limb increases coactivation and joint stiffness (Quartarone et al., 2008). Dystonia commonly aggravates during voluntary movement (Albanese et al., 2006; Geyer and Bressman, 2006) or postural stress such as standing upright or walking (Yanagisawa et al., 1972). Here, the activity-aggravation outcome measure was the lowest active torque of the two muscles during voluntary antagonist muscle activation, i.e. the coactivation outcome measure, multiplied by the lowest active torque of the muscles during the section where no input was given. Coactivation in rest is a prerequisite for activity-aggravation, hence the product.

3. Results

3.1. Model simulations

Fig. 3 presents the simulation results of the reference condition: (arbitrary) normal reflexes and the simulation results with only passive structures, so without any reflexes. Additionally, simulations are presented where one-by-one the feedback pathways are deactivated to demonstrate their separate contributions to the observed limb behavior.

Normal reflexes showed increased stiffness together with slightly more oscillation in respect to no reflexes. These oscillations resulted from the decreased stability margin as introduced by the reflex latencies (i.e. neural time delays) and became more evident without velocity feedback, which acts like damping.

In a sensitivity analysis, muscle, sensory and neural properties in the model were systematically varied to verify that the findings do not abundantly depend upon the initial state. One by one each parameter was simulated at values that were 10% higher and 10% lower than its nominal value, with all other parameters kept to their nominal value. The main effects observed in the simulated reflex scenarios were not susceptible to these variations of the initial conditions. Although the parameter changes slightly modified the scores on the criteria, still the same criteria for fixed dystonia were satisfied. Additionally, simulations with high levels of imbalanced supraspinal input were done to determine whether fixed dystonia could be explained through voluntary control. High levels of cocontraction were attained; however, due to the missing feedback stabilization (Van Doornik et al., 2009), the diminished capacity for voluntary control and the abnormal posture could not both be satisfied.

3.2. Case: fixed dystonia

The abnormal reflex scenarios resulted in a wide range of dysfunctional motor behaviors. The increased reflex sensitivity scenario affected both muscles equally and as such balanced the limb to the neutral position, with either a rigid posture (increased force sensitivity) or fast, oscillatory movements (increased sensitivity to velocity or position), see Fig. 4. The imbalanced reflex offset scenario affected only one of the muscles and did result in abnormal postures (Fig. 5), however, did not explain all other characteristics of fixed dystonia (Table 3). The imbalanced reflex sensitivity to muscle force resulted in behavior that closely resembled all features of fixed dystonia (Fig. 6). Fig. 7 illustrates the abnormal posture and high levels of cocontraction that resulted from imbalanced muscle force feedback. The degree of imbalance determined the severity of the deviation, since force imbalance can only be counteracted by force contributions in response to muscle stretch in the antagonist originating from passive structures and afferent feedback of position (k_p).

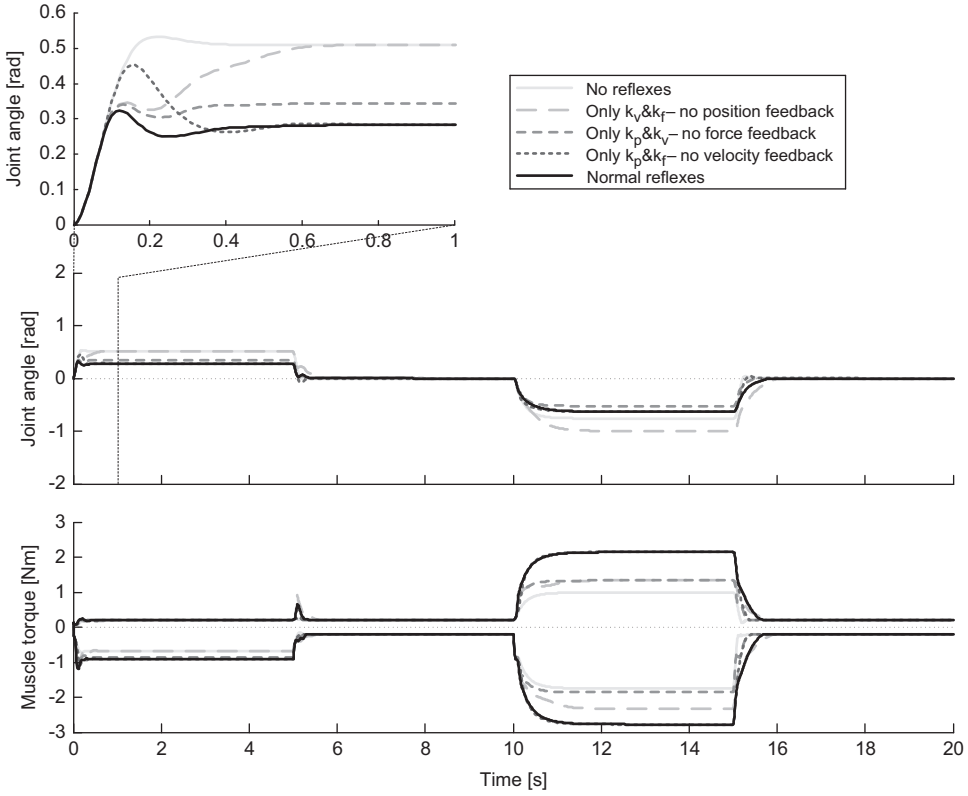

Fig. 3. Model simulation results of the reference conditions. Joint angles (upper panel) and agonist and antagonist muscle torques (lower panel) in response to external force (0–5 s) and voluntary contraction (10–15 s) with normal reflexes (solid black) and without reflexes (solid light gray). Additionally the normal reflex condition is presented, with each of the three pathways disabled to show their separate contributions (dashed). In periods of rest (5–10 and 15–20 s) the muscle contractions subside and the arm returns to its neutral position. The first 2 s of the results are zoomed in to better illustrate the differences in the external force step response.

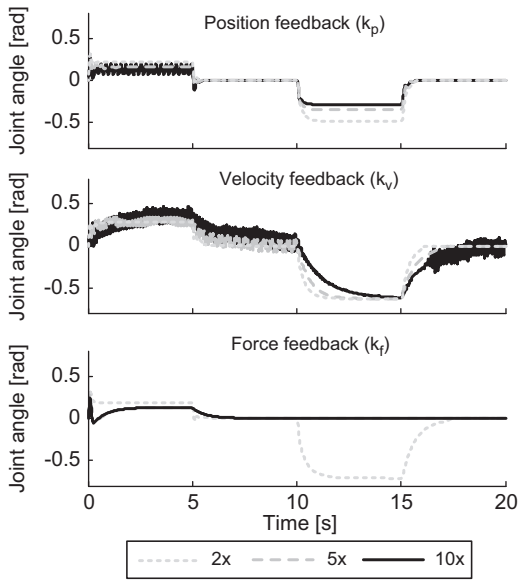

Fig. 4. Model simulation results of the joint angles in response to external force (0–5 s) and voluntary contraction (10–15 s) with the increased reflex sensitivity scenario applied to the three reflex pathways. The top panel presents the scenario applied to position feedback, middle panel to velocity feedback, and the bottom panel to force feedback. The traces represent several multiplication factors of the default gain: light gray dashed trace, 2 × ; dark gray dashed trace, 5 × ; black solid trace, 10 × .

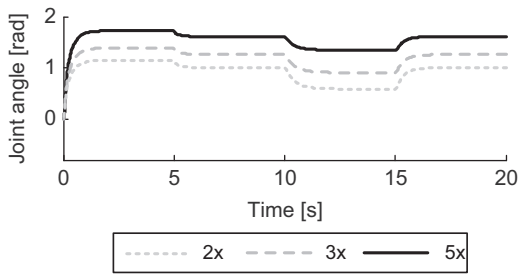

Fig. 5. Model simulation results of the joint angles in response to external force (0–5 s) and voluntary contraction (10–15 s) with the imbalanced reflex offset scenario. Due to summation of the reflexive inputs applying the scenario to the three reflex pathways results in the same behavior. The traces represent several multiplication factors of the default offset: light gray dashed trace, 2 × ; dark gray dashed trace, 3 × ; black solid trace, 5 × .

Modeled behavior that resembled dystonia showed a deviant joint angle in rest (abnormal posture), high muscle contraction levels (sustained muscle coactivation), high resistance to movement (increased joint stiffness), little or no voluntary movement (diminished capacity for voluntary control) and increased coactivation with voluntary control (activity-aggravation). Since no objective thresholds for the criteria exist yet, we chose to use a statistical measure and rated the best quartile of every criterion to fulfill the feature. Table 3 presents the thresholds at the bottom and all values beyond the thresholds are in bold with the number of fulfilled criteria summed to an overall rating on the right. For convenience, Table 4 illustrates which conditions fulfill which criteria. The only condition that satisfied all criteria of dystonia is the imbalanced sensitivity to muscle force feedback. Other conditions that satisfied several of the criteria are imbalanced reflex offset which only limited voluntary control for extremely high offsets and did not actively stabilize the joint around the abnormal posture; increased reflex sensitivity to position or velocity, which did not result in a rigid abnormal posture, but remained oscillating; and increased reflex sensitivity to force, which satisfied all criteria except for the abnormal posture.

4. Discussion

Neuromuscular modeling can be a valuable tool in developing and testing hypotheses on the underlying mechanisms of movement disorders. When properly validated, these models may prove vital for development of new therapies or medications, since radical new procedures can be extensively tested on the models (Tanaka, 2010). Here we developed a model of the wrist joint with spinal reflexes and we identified which reflex pathways potentially explain the clinical features of fixed dystonia.

4.1. Case: fixed dystonia explained by abnormal proprioceptive reflexes

Imbalanced reflex sensitivity for muscle force feedback resulted in behavior which resembled fixed dystonia on all accounts: abnormal posture, sustained muscle coactivation, increased joint stiffness, diminished capacity for voluntary control and activity-aggravation. Moreover it was found that the degree of force feedback imbalance determined the severity of the abnormal posture, which corresponds to the suggested involvement of feedback stabilization to achieve the mid-range postures as reported by Van Doornik et al. (2009). Involvement of abnormal force feedback in fixed dystonia corresponds to preliminary results of reflex identification experiments on patients with dystonia performed by our group, in which reduced inhibitory force feedback was found in patients.

With imbalanced reflex sensitivity to force, activation of the agonist muscle resulted in simultaneous (co)activation of the antagonist, a characteristic feature in dystonia (Geyer and Bressman, 2006). This observation signifies that a-selective activation of muscles in dystonia is not necessarily supraspinal. Previous studies that associate reflex muscle activation to dystonia specifically approach the reflex activity on top of already (co)activated muscles. This study relates the two by explaining the high levels of cocontraction through altered reflexes. Similar to the hypothesis that Levin and Feldman (1994) proposed for spasticity, hypertonus is explained through abnormal reflexive activity; however, our model incorporates an imbalance to explain the abnormal posture in fixed dystonia and narrows down the involved reflex pathways to force feedback. The model could explain all the features of fixed dystonia at the level of spinal control. However, this does not rule out the possibility that the cause for fixed dystonia is rooted higher in the CNS.

Literature suggests that although altered cortical function is associated with the motor impairment in dystonia, it is probable that the primary abnormality is caused by impairment of the basal ganglia circuitry (Berardelli et al., 1998; Bhatia and Marsden, 1994; Gernert et al., 1999; Hallett, 1993, 1998a, b; Sanger, 2003; Van Doornik et al., 2009). Speculatively these structures improperly control the spinal reflexes leading to fixed dystonia. Transcranial magnetic stimulation studies also suggest that in focal dystonia decreased intracortical inhibition by probably GABAergic neurons may lead to increased primary motor cortex excitability (Chen et al., 1997; Ikoma et al., 1996; Mavroudakis et al., 1995; Ridding et al., 1995a, b). Altered GABAergic inhibition may play an important role in the symptomatology of dystonia (Levy and Hallett, 2002; Van Hilten et al., 2000) and may have its effect at several levels of the CNS.

Dystonia represent a complex set of disorders characterized by functional alterations in the sensorimotor circuitry that integrates sensory input and motor output (Breakefield et al., 2008). Breakefield et al. related dystonia and unbalanced sensorimotor pathways: “The sensorimotor circuitry can be disrupted at many levels and by multiple causes, resulting in a precariously balanced substratum state so that ‘second hits’, such as environmental

Table 3
Results outcome measures. All values beyond the best quartile thresholds at the bottom are in bold. The number of fulfilled criteria are summed to an overall rating on the right.

Scenario	Applied to…	Multiplication factor	Posture (rad)	Stiffness (Nm/rad)	Coactivation (Nm)	Voluntary (rad)	Activity (Nm^2)	Rating 0–5
No reflexes	k_p, k_v, k_f	0	0.00	2.0	0.2	0.76	0.0	0
Normal reflexes	k_p, k_v, k_f	1	0.00	3.5	0.2	0.63	0.3	0
Increased reflex sensitivity	k_p	2	0.00	4.7	0.2	0.48	0.4	0
		3	0.00	5.4	0.2	0.41	0.4	0
		5	0.00	6.3	0.2	0.34	0.5	0
		10	0.00	**7.9**	0.2	0.28	0.5	1
		50	0.00	**16.0**	0.2	**0.18**	0.6	2
	k_v	2	0.00	3.5	0.2	0.63	0.3	0
		3	0.00	3.5	0.2	0.63	0.3	0
		5	0.01	3.6	1.2	0.64	1.9	0
		10	0.10	4.2	**3.6**	0.71	5.7	1
		50	0.00	5.1	**7.9**	0.40	**67.3**	2
	k_f	2	0.00	5.4	0.2	0.71	0.8	0
		3	0.00	**7.7**	**19.2**	**0.00**	**370.0**	4
		5	0.00	**7.7**	**19.2**	**0.00**	**370.0**	4
		10	0.00	7.7	**19.2**	**0.00**	**370.0**	3
		50	0.00	7.7	**19.2**	**0.00**	**370.0**	3
Imbalanced reflex offset[a]	k_p, k_v, k_f	0.5	**0.36**	5.0	0.9	0.75	2.0	1
		1	**0.63**	5.7	1.5	0.62	4.9	1
		2	**1.00**	6.8	2.3	0.41	9.7	1
		3	**1.26**	7.5	2.6	0.35	**12.9**	2
		5	**1.61**	**8.7**	**2.9**	0.26	**14.9**	4
Imbalanced reflex sensitivity	k_p	2	0.00	3.5	0.2	0.48	0.4	0
		3	0.00	3.5	0.2	0.41	0.4	0
		5	0.00	3.5	0.2	0.34	0.5	0
	k_v	2	0.00	3.5	0.2	0.63	0.3	0
		3	0.00	3.5	0.2	0.63	0.3	0
		5	0.00	3.5	0.2	0.63	0.3	0
	k_f	1.5	0.00	3.5	0.2	0.55	0.4	0
		2	0.00	3.5	0.2	0.42	0.4	0
		2.5	0.13	6.5	0.3	0.35	0.8	0
		3	**0.82**	**29.6**	1.9	**0.07**	8.9	3
		3.5	**1.15**	**38.4**	2.5	**0.06**	12.8	3
		4	**1.39**	**44.1**	**2.8**	**0.05**	**14.4**	5
		5	**1.73**	**51.9**	**2.9**	**0.03**	**14.4**	5
Threshold: best quartile			0.25	7.75	2.71	0.22[b]	12.87	

[a] The proprioceptive input to the α-motor neuron is summed in the model; an offset to either one of the proprioceptors affects the modeled behavior equally.
[b] Note that to satisfy the voluntary control criterion the value should be below the threshold instead of above as with the other criteria. For little movement due to voluntary activation reflects a diminished capacity for voluntary control.

insults, physiological stress, toxic compounds or increased sensory input, can tip these predisposed brain regions into an unbalanced, 'dystonic' state." They explain the imbalance by an overrepresentation of body parts in the sensorimotor cortex that becomes perpetuated by feedback re-enforcement. They conclude that the etiologies of the dystonias might fall into several 'camps' acting at different levels of system communication in the brain to unbalance sensorimotor pathways.

Fixed dystonia is consistent and independent of tasks in contrast to task-specific dystonia, like writer's cramp (Chen et al., 1997; Filipović et al., 1997). It is therefore reasonable to assume that in fixed dystonia the affected regions within the CNS are located further down the control hierarchy.

The question remains whether the persistent excitatory force feedback reflects a normal physiological property of sensorimotor circuits or relates to a pathological state of disinhibition. Under physiological circumstances, muscle force feedback has traditionally been considered to be inhibitory and to play an important role in promoting interjoint coordination (Nichols, 1994). Compelling evidence, however, indicates that excitatory force feedback is more widespread than previously considered, playing an important role in reinforcing commands to antigravity muscles to support the increased loads encountered during locomotion (Af Klint et al., 2009; Angel et al., 1996; Duysens et al., 2000; Geyer et al., 2003; Grey et al., 2007; Guertin et al., 1995; Latash, 2002; Pratt, 1995; Prochazka, 1996; Prochazka et al., 1997).

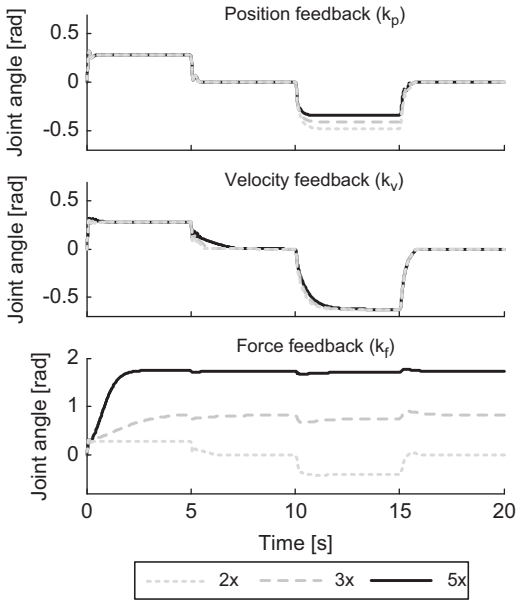

Fig. 6. Model simulation results of the joint angles in response to external force (0–5 s) and voluntary contraction (10–15 s) with the imbalanced reflex sensitivity scenario applied to the three reflex pathways. The top panel presents the scenario applied to position feedback, middle panel to velocity feedback, and the bottom panel to force feedback. The traces represent several multiplication factors of the default gain: light gray dashed trace, 2 × ; dark gray dashed trace, 3 × ; black solid trace, 5 × .

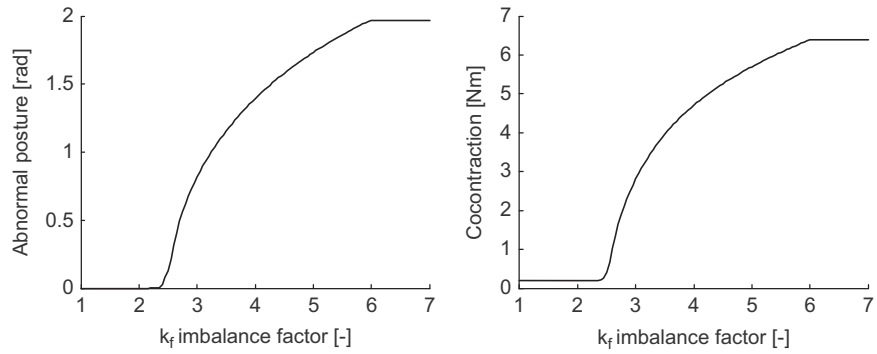

Fig. 7. The abnormal posture (left) and the level of coactivation (right) at rest as a function of the level of imbalance (multiplication factor) in the imbalanced reflex sensitivity scenario applied to the force feedback pathway.

Table 4
Rating of the simulated behavior.

	Increased reflex sensitivity			Imbalanced reflex offset	Imbalanced reflex sensitivity		
	k_p	k_v	k_f	k_p, k_v, k_f	k_p	k_v	k_f
Posture				V			V
Stiffness	V		V	V			V
Coactivation		V	V	V			V
Voluntary	V		V				V
Activity		V	V	V			V

Contrary to inhibitory force feedback which decreases muscle stiffness (Houk, 1972), excitatory force feedback effectively increases the stiffness of the muscle and may be subject to modulation according to the motor task (Mugge et al., 2010; Nichols and Ross, 2009). Muscle force feedback may regulate the mechanical properties of the limb including joint and limb stiffness of the parent muscle and other muscles through neural linkages in the spinal circuits (Nichols and Ross, 2009). In addition, the fact that these pathways are mainly present in specific muscles (anti-gravity) may be a factor in explaining the common postures in CRPS-related dystonia.

The simulations demonstrate that the abnormal posture depends on the degree of imbalance of the force feedback pathway. Theoretically, a positive feedback loop, like force feedback, is (locally) unstable when the loop gain is greater than unity. Given the parameter values in our model, the force feedback loop becomes unstable for a k_f-value of 2.5 times the default value. Note that overall joint behavior remains stable as a result of the other feedback pathways. This study suggests that to explain all the features of dystonia, the force feedback has to be unstable in one of the antagonists.

4.2. Limitations

The case model results are fairly robust to changes of muscle parameter values and even with inactive velocity and position reflex pathways, the imbalanced force feedback scenario resulted in dystonia-resembling behavior, indicating that activity of the other reflex pathways is not crucial.

However there are several limitations that should be acknowledged: First, the threshold values for the criteria should be objectified by means of in vivo experiments. Second, the model is 1 DoF, while the wrist joint has in fact 2 DoF. Since a second DoF can be run in parallel, expanding the model to 2 DoF will not augment our insight into motor control and as such neither into the mechanisms behind dystonia. Moreover, the flexion–extension direction is clinically more relevant in dystonia as the dominant pattern is flexion (Munts et al., 2011). Third, the model is a rather crude representation of neural control of muscles and the muscle moment arms are assumed to be posture independent, an assumption that is not fully justified with large movements. Implementation of higher neural control mechanisms like reciprocal inhibition may improve fidelity, but is not expected to affect the conclusion, since reciprocal inhibition requires muscle lengthening (Nichols and Ross, 2009), while in dystonia the posture is fixed. Expanding the model to include more advanced neural control may be done as future work and may add to our understanding and possibly to other possible explanations for fixed dystonia. Nevertheless, the current study shows that assuming the features are caused at a spinal level, then abnormal force feedback is most likely to explain fixed dystonia as it mimics fixed dystonia remarkably well.

Conflict of interest statement

We declare that we have no proprietary, financial, professional or other personal interest in any product, service and/or company that could be construed as influencing the position presented in, or the view of, the manuscript.

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Appendix A. Neuromuscular model

The neuromuscular model includes a muscle–tendon complex, spinal afferent feedback and passive limb dynamics. The model inputs are supraspinal input n_s and external torque T_{ext}.

The muscle–tendon complex is based on the work of Winters and Stark (1985) and adopted from Stroeve (1996). The muscle–tendon complex consists of a contractile element (CE) representing the sarcomeres, a series elastic element (SE) representing the passive visco-elastic properties of the tendon and aponeuroses, and a parallel element (PE), representing the connective tissues. The CE has a Hill-type force-velocity and force–length dependence and contains first-order excitation dynamics and non-linear

first-order activation dynamics. It receives the lumped continuous neural input from the spinal cord (u), scaled between 0 and 1, representing the neural firing rate of the whole population of α-motoneurons. The neural input to the muscle–tendon complex is the sum of voluntary supraspinal input (n_s) and afferent feedback of velocity (n_v), position (n_p) and force (n_f), representing Ia, Ib and II-afferents. The output of the muscle–tendon complex is total muscle force F which converted to torque using the moment arm r and added to the external torque T_{ext} serves as input to the passive limb dynamics. The mechanical relation between the two muscles ($i=1,2$) is defined by the following set of equations:

$$l_1 = l_0 - r_1\theta$$
$$\dot{l}_1 = -r_1\dot{\theta}$$
$$l_2 = l_0 + r_2\theta$$
$$\dot{l}_2 = r_2\dot{\theta}$$
$$\ddot{\theta} = \frac{T_{ext} + F_1 r_1 - F_2 r_2 - B_l\dot{\theta} - K_l\theta}{I_l}$$

with θ the limb angle, $\dot{\theta}$ angular velocity, $\ddot{\theta}$ angular acceleration, r_i muscle moment arm, F_i force, l_0 muscle rest length, l_i muscle length, $\dot{l}_i$ muscle velocity, r_i moment arm, I_l inertia of the limb and B_l damping and K_l stiffness of surrounding tissues. Muscle force F for each muscle equals:

$$F = F_{pe}(l_m) + F_{se}(l_m, l_{ce})$$

with F_{pe} the force exerted by the PE, F_{se} the force exerted by the SE, l_m the total muscle length and l_{ce} the length of the CE. For the outcome measures of the cocontraction and the activity criteria only the active muscle force (F_{se}) was used to exclude passive contributions (F_{pe}):

$$F_{pe}(l_m) = \begin{cases} 0 & l_m \le l_{pe0} \\ \frac{F_{max}}{e^{PE_{sh}}-1}(e^{(PE_{sh}/PE_{xm})(l_m - l_{pe0})} - 1) & l_m > l_{pe0} \end{cases}$$

and

$$F_{se}(l_{ce}, l_m) = \frac{F_{max}}{e^{SE_{sh}}-1}(e^{(SE_{sh}/SE_{xm})l_{se}} - 1)$$

With l_{se} the length of the SE and l_t the zero-length of the tendon.

$$l_{se} = l_m - l_{ce} - l_t$$

The length of the CE (l_{ce}) is integrated from the velocity of the CE ($\dot{l}_{ce}$) determined from

$$\dot{l}_{ce} = F_{vce}^{-1}(a, l_{ce}, l_m)$$

With $F_{vce}^{-1}(a, l_{ce}, l_m)$ the inverse force–velocity relation of the CE, and activation a determined from

$$\dot{e} = (u - e)/\tau_{ne}$$
$$\dot{a} = (e - a)/\tau, \quad \tau = \begin{cases} \tau_{ac} & e \ge a \\ \tau_{da} & e < a \end{cases}$$

With neural input u:

$$u = \begin{cases} u_t & 0 \le u_t \le 1 \\ 1 & u_t > 1 \end{cases}$$
$$u_t = n_s + n_p + n_k + n_f$$

The afferent contributions to the neural input are defined as feedback gains multiplied by time-delayed muscle states:

$$n_p = \begin{cases} k_p(l_{ce}(t - \tau_{ms}) - l_{ce0}) & l_{ce} \ge l_{ce0} \\ 0 & l_{ce} < l_{ce0} \end{cases}$$
$$n_v = \begin{cases} k_v\dot{l}_{ce}(t - \tau_{ms}) & \dot{l}_{ce} \ge 0 \\ 0 & \dot{l}_{ce} < 0 \end{cases}$$
$$n_f = k_f F_{se}(t - \tau_{gto})$$

The inverse force–velocity relation of the CE ($F_{vce}^{-1}(a, l_{ce}, l_m)$):

$$F_{vce}^{-1}(a, l_{ce}, l_m) = \begin{cases} \frac{V_{sh}v_{max}(a, l_{ce})(F_{vce}(a, l_{ce}, l_m) - 1)}{F_{vce}(a, l_{ce}, l_m) + V_{sh}} & 0 \le F_{vce} \le 1 \\ \frac{-V_{shl}V_{sh}v_{max}(a, l_{ce})(F_{vce}(a, l_{ce}, l_m) - 1)}{F_{vce}(a, l_{ce}, l_m) - (1 + V_{sh}V_{shl})(V_{ml} - 1) - 1} & 1 < F_{vce} \le V_{ml} \end{cases}$$

Using the relative force of the CE due to the force–velocity relation (F_{vce}):

$$F_{vce}(a, l_{ce}, l_m) = \frac{F_{se}(a, l_{ce}, l_m)}{aF_{max}F_{lce}(l_{ce})}$$

And the maximum velocity of the CE (v_{max}):

$$v_{max}(a, l_{ce}) = V_{vm}(1 - V_{er} + V_{er}aF_{lce}(l_{ce}))$$

With the relative force of the CE due to the force–length relation (F_{lce}):

$$F_{lce}(l_{ce}) = e^{-((l_{ce} - l_{ce0})/l_{cesh})^2}$$

All other symbols denote (constant) muscle parameters which are specified in Table 1.

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